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Modelling the epidemiology and economics of sheep scab in Great Britain

Modelling the epidemiology and economics of sheep scab in Great Britain

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Abstract

Sheep scab is an important parasitic disease of livestock, particularly sheep, found worldwide. In Great Britain, its prevalence has grown steadily since reintroduction in 1973, despite attempted national control prior to 1992 and a number of industry-led interventions. Recent reports of resistance in the causative agent, the mite *Psoroptes ovis*, to macrocyclic lactones, increases importance of urgent coherent action. The aim of this thesis was to develop epidemiological and economic models for sheep scab in Great Britain that could provide tools able to identify better scab management strategies.

A within-farm transmission model was developed, based on the classic SIR model used widely in epidemiology (Chapter 2). Model results show that 100 days after the introduction of one scab index case, around 80% of a flock are likely to be infected. Sensitivity analysis suggests that the transmission rate is the most important parameter to target in future interventions.

The model was expanded into a metapopulation model, with transmission across Great Britain possible via neighbour-to-neighbour contact (Chapter 3). Farm clusters with high connectivity and transmissibility are identified, which could be targeted in future interventions. Model simulation results show that scab spreads rapidly when introduced into one of these clusters, however, it is then limited to the cluster edges, suggesting that scab is unlikely to spread across the whole of Great Britain by neighbour-to neighbour contact only and that long distance movements may be important future intervention targets.

The within-farm model is revisited in Chapter 4 and an additional compartment is added for carriers of scab. The newly parameterised model produces output which is shown statistically to be from the same distribution as experimental data.

These changes are carried into Chapter 5, where an alternative metapopulation model is presented. Approximate Bayesian Computation is used to fit this model to reported data. The importance of long-distance movements is confirmed and evidence for the importance of the timings and synchrony of treatment on the seasonality of scab dynamics is provided.

An economic game theory model looking at the prophylactic treatment choices of two farmers found that it is currently not cost-effective to use prophylaxis for scab in Great Britain, except when the risk is high and treatment costs are low (Chapter 6). Lower insecticide costs or subsidies would be required to incentivise farmers to treat prophylactically.

The models provide tools that, with further scenario analyses, could help shape effective and economical interventions for scab control.

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Author's declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

SIGNED: ..... DATE:.....

Table of contents

Chapter 2- A basic model for within-farm transmission of sheep scab

Chapter 3- Modelling the spatial dynamics of sheep scab across Great Britain

Appendix I

Nixon, E., Rose Vineer, H. & Wall, R., 2017. Treatment strategies for sheep scab: An economic model of farmer behaviour. *Preventive Veterinary Medicine,* 137(A), pp. 43-51.

Appendix II

Supplementary material from Chapters 2 to 5.

List of Figures

List of Tables

Chapter 1

THE EPIDEMIOLOGY AND ECONOMICS OF SHEEP SCAB AND THE ROLE OF MODELLING IN ITS STUDY

1.1 INTRODUCTION

Mathematical modelling can provide insight into the epidemiology of a disease (Keeling & Rohani, 2008) and thus can contribute towards improving control methods (Alvarez et al. 2019). Understanding more about the economic drivers in farmer decision making is also important when improving current control methods (Farm Animal Welfare Committee, 2011). The overarching aim of this thesis was to develop epidemic and economic models of ovine psoroptic mange (sheep scab) transmission and farmer behaviour and use these to consider current transmission and future management of scab in Great Britain, ultimately reducing the sociological, economic and environmental impact of this disease.

The livestock sector contributes to forty percent of global agricultural production (World Bank, 2009) and by 2050, it is predicted that the international demand for livestock products will have doubled in size (FAO, 2006). It is estimated that millions of pounds per year are lost globally through parasitic diseases of livestock (Lopes et al., 2015). This has particular impact on those living in poverty, of whom 1 billion rely on domestic livestock to meet their financial and dietary needs (Grace et al., 2012). As well as having an economic impact, parasitic diseases in livestock have wide social and environmental impacts, including environmental residues, increased greenhouse gas emissions and increased water consumption, plus parasiticide resistance and animal welfare issues (Rushton & Bruce, 2017). These environmental repercussions may further exacerbate the future impact of livestock parasites and they may spread to regions where they were previously not present (Short et al., 2017) while, along with the development of resistance to some of the main parasiticides, disease prevalence will increase in the future unless new treatments can be developed (Geurden et al., 2015; Doherty et al., 2018).

Ovine psoroptic mange (sheep scab) is an important livestock parasitic disease caused by a hypersensitivity response in sheep (*Ovis aries*) to the faecal material of the parasitic mite *Psoroptes ovis* (Hering) (Burgess et al., 2012b). This ecto-parasitic condition impacts sheep farming systems worldwide and is found on almost every continent (Fig. 1.1). In the United Kingdom (UK), where 71% of land is used for agriculture (Department for Environment, Food and Rural Affairs- DEFRA, 2016), sheep scab is endemic and in Great Britain it has been estimated to cause losses of 8 million pounds sterling per year (Nieuwhof & Bishop, 2005). Considering that mutton and lamb production in the UK is valued at 1.1 billion pounds sterling annually (Department for Environment, 2016) and that this estimated loss is likely to be an underestimate (Nixon et al. 2017), sheep scab can be considered to be a significant economic and animal welfare issue in Great Britain.

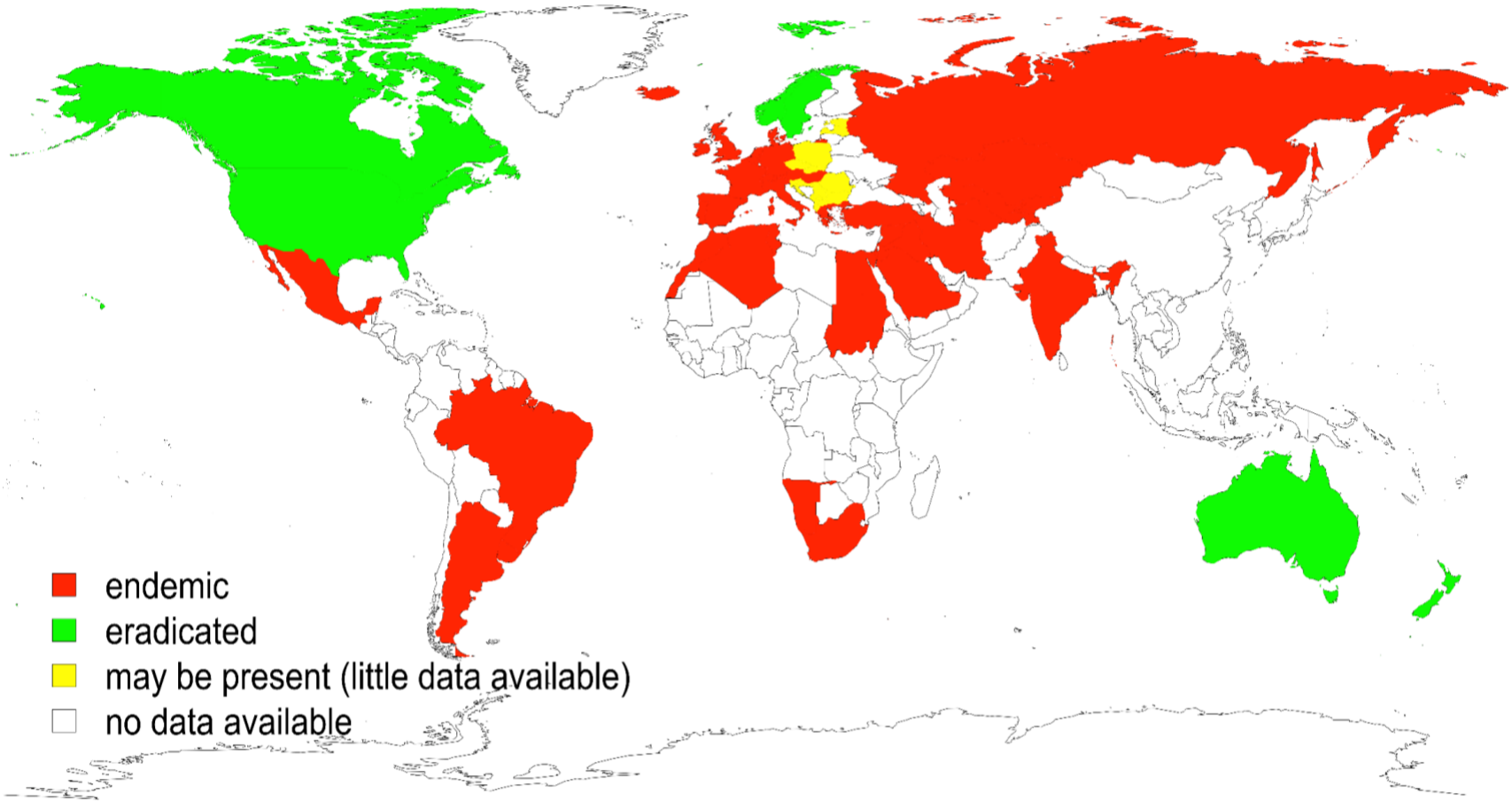

Fig. 1.1 Status of sheep scab worldwide. This was produced using information from a literature review by the Agricultural Development Advisory Service (ADAS) (2008). Yellow countries ("may be present") are central and eastern European countries that were not specified by name, but which are thought to be included in the claim made by the literature review that scab is endemic in "most central and eastern European countries".

1.2 AETIOLOGY AND PATHOGENESIS

1.2.1 *Psoroptes ovis* - the causal agent of sheep scab

1.2.1.1 History

Although sheep scab is a condition which is thought to have been documented in texts as ancient as the Old Testament (Leviticus 22:22, New International Version) and by ancient scholars (Cato, Virgil, Pleno and Columnella (Kirkwood, 1986; ADAS, 2008)), a mite was not confirmed as the causal agent of the condition until 1809 (Walz, 1809). This mite, *P. ovis,* was named by Hering in 1835 and its life cycle determined by Gerlach in 1857 (Gerlach, 1857) (Fig. 1.2). It is a member of the family Psoroptidae, order Asitgmata.

1.2.1.2 Life cycle

The lifecycle of *P. ovis* (Fig. 1.2) takes place entirely on the host and consists of five stages: egg, larva, protonymph, tritonymph and adult (Sweatman, 1958). When conditions are optimal, the full life cycle can take 11-19 days (Downing, 1936; Sweatman, 1958). Adult female mites measure about 1mm in length (Lewis, 2013) and adult males 0.38mm (Sanders et al. 2000) (Fig. 1.3). Two days after adult females have emerged, they start oviposition, which lasts for up to 29 days, with 1-6 eggs being deposited per day (15-30 eggs in total). In some cases, when conditions are favourable, they have been known to deposit up to 90 eggs. Adult males and females survive for 11 to 42 days (Stockman & Berry, 1913; Shilston, 1915; Downing, 1936).

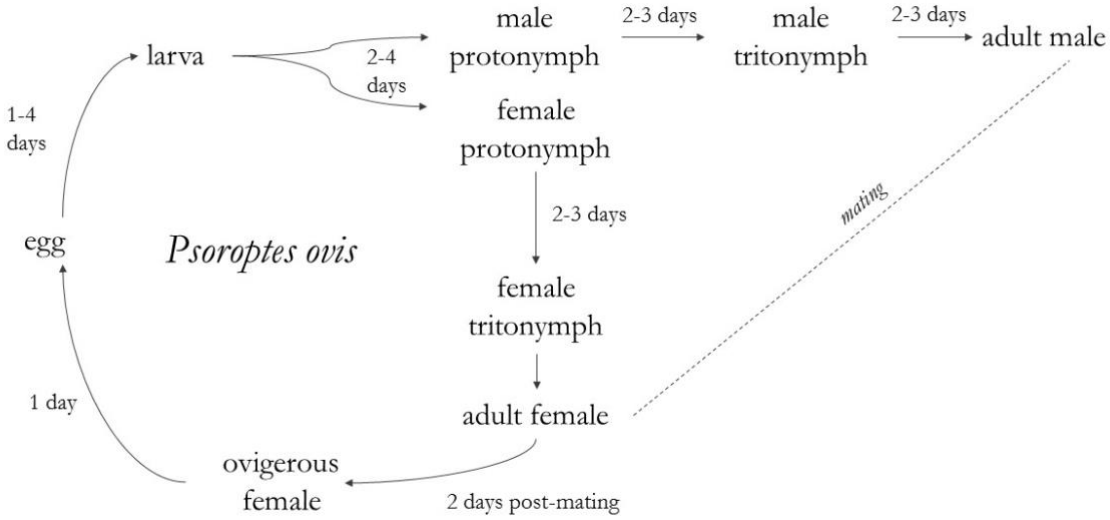

Fig. 1.2 Lifecycle of the *Psoroptes* mite (the causal agent of sheep scab) as determined by Gerlach (1857). The durations shown here are averages of the studies which have observed the life-cycle on the host (Gerlach, 1857; Stockman & Berry, 1913; Shilston, 1915; Babcock & Black, 1933; Downing, 1936; Lucas, 1942; Kemper & Roberts, 1950).

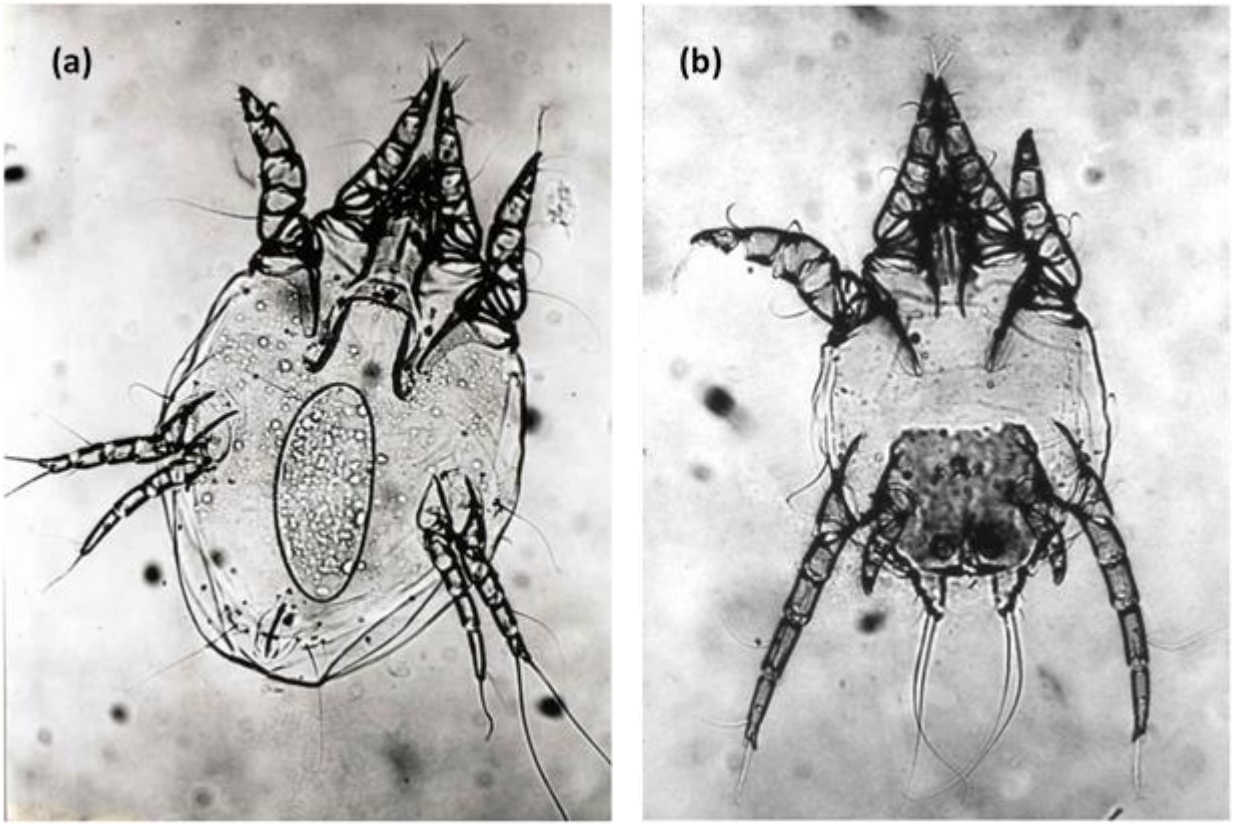

Fig. 1.3. Light micrographs of a female (a) and male (b) Psoroptes ovis mite.
Photos courtesy of Richard Wall.

1.2.1.3 Feeding

Psoroptes ovis do not burrow or pierce the skin of the host but remain on the skin surface (Kirkwood, 1986). Here, adult mites will feed on lipids and skin debris (such as shed epithelial cells) (Bates, 1997a). The feeding action of *P. ovis* was formerly thought to trigger the clinical pathology seen in sheep scab (Downing, 1936), however this has since been attributed to a hypersensitivity response in sheep to antigens in the faeces of *P. ovis* mites and to secondary bacterial infections. This antigenic material can include the petritrophic membrane, gut flora, guanine and a range of proteins homologous to allergens and antigens found in the house dust mite (Matheison & Lehane, 1996; Bates, 1997a; van den Broek & Huntley, 2003b). As a result of the hypersensitivity response; serous exudate is excreted onto the skin surface by an infected and symptomatic host and this provides nutrition for *P. ovis* in addition to which the surge in temperature and humidity at the skin surface of the host following the inflammation provides a suitable micro-climate for *P. ovis* (Bates, 1997a).

1.2.1.4 Off-host survival

Adult *P. ovis* mites have been reported to be able to live off the host for a maximum of 38 days (Babcock & Black, 1933). However, they may only be able to re-infect sheep for 15-16 days off-host depending on humidity and temperature (O'Brien et al., 1994). This is significant in terms of disease control, as transmission does not only occur via sheep to sheep contact (direct transmission), but also via sheep contact with *P. ovis* mites in the environment (indirect transmission). It has been suggested that wool tags on fencing (Fig. 1.4) or on other fomites may be important environmental sources of transmission for *P. ovis* (Henderson, 1990; van den Broek & Huntley, 2003b), allowing for transmission between neighbouring flocks, flocks which share the same equipment or to susceptible flocks which move to an area that was recently inhabited by an infested flock. However, there have been no studies which provide data on the importance of wool tags in sheep scab transmission.

Fig. 1.4. Wool tags on fencing.

1.2.1.5 Host specificity

The host-specificity of isolates within the *Psoroptes* genus has been under debate for many years (Wall & Kolbe, 2006; Losson, 2012). Until recently, the nomenclature of *Psoroptes* mites followed Sweatman's (1958) classification; he argued that there were five species (*P. cuniculi, P. cervinus, P. equi, P. natalensis* and *P. ovis)* within the genus, classified according to the host infested, the morphological differences seen between mite populations on different hosts and the mite infestation site on the host. *Psoroptes* mites subsequently found on other hosts were named in a similar fashion, for example, *P. pienaari* found in African Buffalo (Fain, 1970) and *P. auchinae* found in alpacas (Foreyt et al. 1992). However, experiments have suggested that mites collected from different hosts are able to mate and produce viable offspring (Wright et al. 1983) (although this has never been repeated) and phylogenetic studies comparing ITS1 and ITS2 sequences have shown that *Psoroptes* mites are unlikely to be genetically host specific (Zahler et al., 1998; Ochs et al. 2001; Pegler et al., 2005). It is therefore now more commonly accepted that, although there are morphological differences observed between *Psoroptes* mites on different hosts, these are most likely to be phenotypic variants within a species resulting from

adaptations to particular micro-environments, rather than separate species (Bates, 1999; Zahler et al., 2000; Pegler et al., 2005). In terms of disease transmission, this raises concerns about the possible transmission of *P. ovis* to sheep from other livestock or from wildlife. However, if it occurs at all, it is likely to be very rare and would require close contact between animals (Losson, 2012). In addition, it is often the case that *P. ovis* is endemic in only one livestock species within a country. For example, in the UK it is endemic in sheep, but rare in cattle. Conversely, in Belgium, it is common in cattle, but rare in sheep (Losson et al., 1999). Therefore, a lack of host-specificity of *P. ovis* is not currently considered to be an issue of epidemiological significance.

1.2.2 Clinical signs of sheep scab

Skin lesions caused by the hypersensitivity response cause minor to moderate pruritus, resulting in head tossing and sheep rubbing, scratching and biting at affected sites (Sargison et al., 1995; Bates 1997a). The pruritus increases over the course of the disease along with the staining and matting of the fleece on affected areas of skin, which eventually drops off. Self-trauma of the now-exposed areas leads to abrasions and secondary bacterial infections (Sargison et al., 1995). A nibble reflex is associated with the condition, which manifests in tongue protrusion and lip smacking (Bygrave et al., 1993). Mortality usually results from the secondary bacterial infections, condition loss, hyperthermia (Bates, 2007) or stimulation which leads to epileptiform convulsions (Bygrave et al., 1993).

1.2.3 The Phases of sheep scab

There is a wide individual variation in clinical response to infestation by *P. ovis*, even within the same sheep breed and in the same geographical location (Matheison & Lehane, 1996). However, general trends have been observed in the pathology, which were divided into phases by Bates (1997a) based on three specifications over time: (1) lesion area, (2) adult female population size observed around lesion edges, and (3) the anti-*P. ovis* IgG titre (deduced using an enyzme-linked-immunosorbent-assay - ELISA).

It has been suggested that an infestation of *P. ovis* mites can be initiated by a single ovigerous female (van den Broek & Huntley, 2003b). An inflammatory response is initiated within hours and clinical signs such as lesions and increased rubbing may appear as early as 2 days post-infestation (Kirkwood, 1980). However, in many animals, clinical signs may not be apparent for several days while mite numbers are low. Experiments described by Babcock and Black (1933) have shown that the time between experimental introduction of mites and clinical signs of infestation can vary from 12 to 51 days. If clinical signs do appear, they are in the form of small, raised vesicles containing clear serous fluid, which can leak and dry, forming a yellow scab about 1 cm in diameter. Infected hosts may be restless, rub more frequently against fences, have stained areas of wool and toss their heads. The duration of this initial phase may vary from case to case; for a 'medium virulent' *P. ovis* strain in artificial infestations by the Central Veterinary Laboratory, the pre-clinical phase lasted for up to 25 days (Bates, 1997a). The clinical signs of the initial phase can also be seen in sheep with other parasitic infestations such as blowfly strike (*Lucilia spp.*), chewing lice (*Bovicola ovis*) or scrapie and so it can be difficult to diagnose sheep scab in this phase (Bates, 1997a).

Following this initial phase, the population of mites increases, lesions expand and spread and there are higher levels of IgG detected in the blood. The serous exudate from lesions dries and forms scabs, wool loss may be seen and open wounds may form. Increased rubbing and head tossing may occur. This phase is also when epileptiform fitting is sometimes seen (Bygrave et al., 1993).

In some cases of scab, the population of *P. ovis* may then stabilise for a time. During this time the lesion area and the antibody titre can still increase and the infested animal may die. In other cases, lesion growth may slow or cease. When this occurs, the immune response of the sheep and the reduced availability of feeding sites means that the mite population may start to decrease rapidly. More specifically, the immune response is thought to be made up of specific immunoglobulin and leucocytes which target the mite mid-gut cells, consequently preventing uptake of nutrients and therefore egg production (Stromberg & Fisher, 1986). There can still be antibody titres during this phase because mite faeces are still in contact with the skin and consequently provoke an immune response in the sheep. Secondary bacterial infections can occur during this phase. It is

thought that approximately two thirds of sheep infested with scab left untreated will survive (Babcock & Black, 1933; O'Brien, 1995). In these cases, the mite populations die out, new wool grows, and scabs lift away from the skin. In some cases, however, some mites may still survive on the host, even though it is no longer displaying any clinical signs. They usually survive under any remaining dry scabs or in 'cryptic sites'. Cryptic sites may include the pinnae, the external auditory canal, the perineum, the inguinal fossae and the infra-orbital fossae. *P. ovis* mites located in the external auditory canal can survive plunge dipping (one of the main treatment methods for scab- see section 1.4.2).

1.3 DIAGNOSIS

The diagnosis of sheep scab can be difficult, as the clinical signs are not always apparent until the more advanced stages of the condition (Bates, 2000); it is particularly difficult during the cryptic stage of scab (Bates, 2009). Delayed or ineffective diagnosis can lead to undetected transmission between individuals in a flock and between flocks. Therefore, research into the improvement of sheep scab diagnosis is crucial.

Traditionally, sheep scab has been diagnosed via clinical observation and microscopic detection of mites from wool and skin scrapings (Ochs et al., 2001). The addition of potassium hydroxide (KOH) and the centrifugation of skin scrapes can sometimes reveal mites in samples that initially appear to have none (Young, 2016). Even so, this method of diagnosis is not always successful in identifying infection and has been found to have a success rate as low as 18% (Bates, 2009). Unsuccessful diagnosis using microscopy is likely to be particularly common with subclinical infestations (Kirkwood, 1985b) and low numbers of mites (Young, 2016). In addition, simultaneous infestations from other mites can further complicate this diagnostic method (Wells et al., 2012).

However, the development of an enzyme-linked immunosorbent assay (ELISA) for sheep scab diagnosis (Nunn et al., 2011) now allows for scab to be diagnosed at a flock level during the early stages of the disease, in some cases before any clinical signs have been observed (Nunn et al., 2011; Burgess et al., 2012). The current ELISA uses a recombinant form of Pso o 2, a mite protein identified by Temeyer (2002) which gives it a higher specificity than previous *P. ovis* ELISAs for sheep, which were based on crude

extracts of *P. ovis* (Wassall et al., 1987; Boyce et al., 1991; Ochs et al., 2001; van den Broek et al., 2003a). The use of a recombinant protein in the current ELISA, as opposed to complex mixtures of antigens, also allows for higher reproducibility of results. In addition, it can be manufactured without requiring *in vivo* maintenance of mites from an infected host, which reduces production costs and welfare issues, ultimately allowing for higher quantities of the ELISA to be reproduced (Nunn et al., 2011). The sensitivity and specificity of this ELISA has been shown to be 93% and 90% respectively (Nunn et al., 2011), however, more recent developments have allowed it to reach a sensitivity of 98.2% and a specificity of 96.5% (Busin, 2017).

Currently, results from the ELISA test can take up to a week to be returned. Therefore, farmers must either wait a week to find out the result, increasing the impact of scab on the flock if scab is present, or farmers may treat before receiving the results, which, if scab is not present, will be costly and an unnecessary contribution towards increasing resistance of both *P.ovis* and endoparasites to the treatments available (the same treatments are used for both) (Busin, 2018a). The cost of the ELISA is also an issue, since it requires a veterinarian to obtain a blood sample. Hence the cost of the veterinary call-out plus the test costs need to be low enough to make it economical for farmers, who, due to the relative low costs of the acaricides (NOAH, 2010; NOAH, 2017), may choose to apply a blank treatment on suspicion of scab, rather than pay for a diagnosis.

1.4 TREATMENT AND PREVENTION OF PSOROPTIC MANGE IN SHEEP

1.4.1 History of treatment and prevention in Great Britain

Written accounts of treating sheep for skin diseases date back as far as 169 BC, where Cato advised that, after shearing, sheep be smeared with olive oil dregs, wine lees and water from steeping lupins (Cato, 169-160BC). In the Middle Ages, the Winchester pipe rolls (from 1282 onwards) record sheep being salved with mercury, lard, tar, rancid butter and goose fat; it is thought with a purpose to combat sheep scab (Page, 2003).

The first record of a control policy for a sheep disease (thought to be sheep scab) in Great Britain, was initiated by King Hywel Dda in 949AD. He forbade the trading of

scab-affected sheep between November and April and the grazing of sheep on land that had been used by infested sheep up to seven years previously. It seems that these control measures were unsuccessful in preventing sheep scab outbreaks, as in 1297, Hemingburgh (an English chronicler) recorded that the sheep scab epidemic in England had led to near-bankruptcy in Flanders, a city that was economically reliant upon English wool (Urquart, 1983; ADAS, 2008).

There are no records of any other governmental control polices until the 19th Century. However, "sheep washing areas" that date from around the 16th century can still be found in the place names of many parts of Great Britain (Lewis, 2013) and it is thought that washes containing arsenic, lime, nicotine, mercury, or turpentine were used to treat sheep scab until the 19th century (Kirkwood, 1986).

The first commercial dip solutions for sheep scab were developed by William Cooper from 1843 onwards, the most successful being a combination of arsenic and sulphur (Lewis, 2013). These dips had little residual activity and as *P. ovis* eggs were not affected, the dipping had to be repeated 10 days later in order to completely remove individuals from all life stages. The sheep needed to be shorn prior to the dipping and individual sheep were lifted in and out of the dip (which was above ground), making dipping a tedious process (O'Brien, 1999).

Governmental control began again in 1869, when sheep scab was made notifiable and outbreaks started to be recorded. Records show that by 1890, the yearly number of outbreaks was between 1,207 and 3,536 (Watson, 1976). A number of Sheep Scab Orders were given in the following years (Table 1.1). The organochloride acaricide, γ-HCH (lindane), was the first treatment to have a residual activity (up to 3 months) long enough to require only a single dip (O'Brien, 1999). This treatment was used as part of the National Control Programs from 1948 (Table 1.1) and is thought to have greatly contributed to the eradication of sheep scab from lowland flocks by 1940 (Bates, 2006) and in the whole of Great Britain by 1952 (Kirkwood, 1985b).

Unfortunately, scab re-appeared in Great Britain in 1972 via sheep imported from Ireland and, due to misdiagnosis by a new generation of farmers and veterinary surgeons unfamiliar with the clinical signs, it was able to spread across Great Britain undetected until early 1973 (Loxam, 1974; Anon, 1975; Watson, 1976). Various regional and national

treatment programs were enforced in the following years to control scab, including a national autumn and summer dip, a national autumn dip only, a national summer dip only, and regional dipping programmes, but these were unsuccessful in eradicating the disease (French et al., 1999). Up until the 31st December 1984, these treatment programmes still included the use of lindane, but on this date the use of organochloride-based dips became illegal, due to concerns surrounding possible residues in exported lamb (Henderson, 1991). Fortunately, in 1981 and 1982, two organophosphate (OP) dip formulations for scab had been introduced; Diazinon (Kirkwood & Quick, 1981) and Propetamphos (Kirkwood & Quick, 1981) and these became the treatment of choice following the prohibition of organochloride-based dips.

The first non- OP dip, the synthetic pyrethroid (SP), flumethrin, was licensed as a treatment for lice and scab in 1987 (Kirkwood & Bates, 1982). Synthetic pyrethroid (SP) dip use became more popular in the following years. However, by 2008, all SP sheep dips other than cypermethrin were banned due to environmental concerns (ADAS, 2008). Cypermethrin was then banned in 2010 due to its toxicity to aquatic organisms (Anon, 2010).

Table 1.1. Historical sheep scab orders in Great Britain (1898-1948).

Year of Sheep Scab Order	Content	Reference
1898	Local authorities must engage veterinary surgeons to diagnose scab	(Page, 1969)
1905	Local authorities must enforce either a single, double or triple annual dip	(ADAS, 2008)
1907	Sheep must be immersed in dip for 30 seconds	(ADAS, 2008)
1914/1920	Double dipping (dipping must occur again within 10-14 days of the first dip)	(Kirkwood, 1985b; Spence, 1951)
1926	*Amendment of the 1907 order:* sheep must be immersed in dip for 1 minute	(ADAS, 2008)
1928	Disease notification required, compulsory treatment (double dipping) or euthanasia of infected animals in index and neighbouring flocks, dip must be government approved (tar, arsenic, lime-sulphur and tobacco), restricted movement of animals in infested areas	(ADAS, 2008; Spence, 1951)
1948	*Amendment of 1928 order:* organochloride acaricide, γ HCH (lindane) allowed as a single dipping treatment, double dipping still used for the other dipping formulations	(Page, 1969; Spence, 1951)

1.4.2 Current treatment and prevention of scab in Great Britain

From 1992 onwards, sheep scab was deregulated, and the use of preventive treatment for scab was no longer compulsory. This decision was based on the assumption that national sheep scab eradication was unfeasible, expensive and was better dealt with locally by the sheep industry (Ministry of Agriculture Fisheries and Food-MAFF, 1992; ADAS, 2008). Farmers are now left to make their own treatment choices, although the 1997 Sheep Scab Order dictates that it is still compulsory to use reactive treatment when scab is detected (MAFF, 1997) and the Sheep Scab Order of 2010 makes it compulsory to report scab in Scotland (Scottish Government , 2010). From the time of reintroduction in 1972 to 1992, the number of outbreaks per year never exceeded 160 (French et al., 1999), however, post-deregulation the numbers of outbreaks increased to around 7,000 per year (Bisdorff et al., 2006).

Diazinon is the only OP dip still in use today and it is also used to treat other ectoparasites such as lice and blowflies (National Office of Animal Health - NOAH, 2010). Only a single dip is needed and the residual activity lasts for 63 days (Kirkwood & Quick, 1981; O'Brien, 1999), allowing it to be used prophylactically and reactively. Diazinon is most effectively applied as a plunge dip, rather than by using shower dippers, pour-ons or jetting races which have been found to be ineffective (Bates et al., 2005).

As well as OP dips, macrocyclic lactone (ML) injectables are also licenced treatments for sheep scab in the UK. These include the milbemycin, Moxidectin, and the avermectins, ivermectin and doramectin. Ivermectin has no residual activity (Sustainable Control of Parasites in Sheep - SCOPS, 2019). Moxidectin and doramectin do have residual activity which varies with formulation; long-acting Moxidectin (Cydectin LA), for example, has a residual activity of 60 days and only requires a single dose (NOAH, 2017). Due to the residual activity, long acting MLs are used reactively and preventatively.

Since the end of compulsory dipping in 1992, there have been a number of attempts to manage sheep scab by the industry. The Scotland Sheep Scab Initiative, established in 2003, and the Scotland Sheep Scab Industry Working Group which replaced it in 2007, led the development of the Sheep Scab Scotland Order in 2010 (Animal Health and Welfare Wales, 2018). From November 2012 to March 2014 in England, "Stamp out

scab", a project managed by the English Beef and Lamb Executive (EBLEX) and the Agricultural Development Advisory Service (ADAS) (and funded by the Rural Development Programme for England from the Department of Environment, Food and Rural Affairs- DEFRA), aimed to reduce the prevalence of sheep scab by providing detailed training to vets and animal medicines advisors (SQPs) with the hope that they would then pass on this training to farmers in their local region (Phillips et al., 2013). There has been little evidence, to date, to show that this initiative has had any effect on the prevalence of sheep scab in England. In Wales, sheep scab is a priority for the Animal Health and Welfare Framework Group and a report has been recently been published with a proposed strategy towards eradication in Wales (Animal Health and Welfare Wales, 2018).

A questionnaire survey in Wales (Wall et al., 2017) found that injection of MLs (moxidectin, ivermectin or doramectin) was the most popular method for treating scab (85%, n =135), with only 13.3% (n = 21) using OP dips. Other treatments used were Cypermethrin (SP) (0.6%, n =1) and spot-on or herbal (0.6%, n=1). For scab prophylaxis, injection of MLs was still the most popular treatment method (49.7%, n=228), although OP dips were a much more popular method for prophylaxis (40.8%, n=189) than they were for reactive treatment.

1.4.3 Organophosphate dips

There have been a number of concerns that organophosphate dips may have negative effects on the health of the humans who operate the dips (Murray et al., 1992; Stephens et al., 1995; Fletcher & MacLehose, 2005; Sargison et al., 2007; Solomon et al., 2007; Ross et al., 2010; Koureas et al., 2012; Khan et al., 2019).

A literature review investigating whether exposure to OPs impacts mental health outcomes found an association between poor mental health and chronic low-dose exposure to Ops (Khan et al., 2019), although it is acknowledged that the definitions of pesticide exposure in the literature are not consistent. Some studies have found evidence suggesting that operating OP dips can lead to decreases in sperm count and volume (Perry, 2008; Yucra et al., 2008; Recio-Vega et al., 2008; Melgarejo et al., 2015). Others

have found an association between exposure to OPs and neurobehavioural impairment (Solomon et al., 2007; Ross et al., 2010). Most of these studies only show association and cannot confirm that there is a causal link between exposure to OPs and ill-health.

Some studies, however, have provided evidence for a causal link between exposure to OP dips and ill-health. Cherry et al. (2002) and Mackness et al. (2003) both found that amongst those exposed to OP sheep dips, those with symptoms of ill-health also carried the genetic variants of the paraoxnase gene associated with less effective detoxification of organophosphates. This was also found by Povey et al. (2007), who identified particular polymorphisms, GST, CYP and PON1, that might be related to the risk of ill health in sheep dippers (Mackness et al., 2003; Costa et al., 2013; Khattab et al., 2016). However, a study which found a correlation between OP exposure and neurobehavioural impairment, did not find that this correlation could be attributed to PON1 polymorphisms. This suggests that OP dip exposure may not be necessarily be the cause of the neurobehavioral impairment, or that there may be other genetic factors not yet identified that come into play. In addition, it is still unknown whether PON1 status is important at low levels of OP exposure (Costa et al., 2013).

Regardless of the evidence for or against the impact of OP dips on human health, if farmers believe that OP dips are causing a negative effect on health, then this has implications for disease control. When recommending or explaining farmer's treatment choices for sheep scab, their perspective on this issue must be considered, as this will have an impact. As already discussed in section 1.4.2, dips seem to be less popular generally than injection of MLs, which could be attributed to the farmers' perceived risk of dip-use on their health.

OP formulations can enter the environment if spillage occurs during application, through incorrect disposal (Scottish Environment Protection Agency, 2006), through the faeces and urine of treated animals (Roberts & Hutson, 1999) and during wool production (Savage, 1998; Environment Agency, 1999). There are stricter manufacture and formulation guidelines in the EU and USA than in most other regions and so it is thought that the chance of introducing OP formulations into the environment is less likely in those regions (Boxall et al., 2006). However, if correct disposal is costly then farmers are less likely to follow correct procedures (Armstrong & Phillips, 1998).

There is much evidence to suggest that OP sheep dip waste is present in water systems of Great Britain (Littlejohn & Melvin, 1991; Virtue & Clayton, 1997; Environment Agency, 1999; Boxall et al., 2006) and that this negatively impacts aquatic fauna (Giddings et al. 1996; Moore & Waring, 1996). However, there is little data on other environmental impacts of using OP dips on sheep. Of the data that is available, there is little on faecal excretion of OP by sheep (Beynon, 2012b) and so extrapolations must be made from data on faecal excretion of OP by cattle. These extrapolations suggest that using OP dips on sheep may impact adult dung beetle survival (Miller & Pickens, 1973; Blume et al, 1976; Lumaret, 1986). In turn, this may mean that vertebrates with coprophagous prey such as dung beetles may be affected by any residues of OP on the prey (McCracken, 1993; Beynon, 2012b). In addition, the mortality of prey may have an impact on vertebrate predators, but this is not confirmed and the predator may have alternative prey which it can exploit (Beynon, 2012b). In terms of soil fauna, again, there is little data available, however, OP is thought to bind tightly to soil (Cooke et al., 2004) which reduces leaching but may impact soil fauna. The soil microbial community may be impacted, causing some bacteria to thrive, while others to perish, but again there is little data available on this.

Ensuring that farmers have an incentive to correctly dispose of dip waste would help to reduce any impacts of OP dips on the environment. More research needs to be done on the faecal excretion of OPs by sheep to determine whether this might be impacting organisms in the local environment. At the time of writing, there have so far been no reports of resistance in *P. ovis* mites to Diazinon.

1.4.4 Macrocyclic lactones

It is currently thought that application of macrocyclic lactone (ML) injections to sheep has little or no harmful effects on humans. It is thought that significant toxicity in humans only occurs after a large amount of MLs is ingested orally (Yang, 2012).

MLs injected in sheep mainly enter the environment via faeces (Halley et al., 1989a; Vokral et al., 2019). A study in Brazil showed that under subtropical environmental conditions that injected Moxidectin can persist in lamb faeces up to 42 days post treatment and for 88 days after exposure to the environment, whether protected from rain or not (Hentz et al., 2019). Macrocyclic lactone residues have been found at lower

concentrations in environment than for other chemicals used to treat parasitic and bacterial diseases in livestock (Boxall et al., 2006). Other environmental entry points for injected MLs include wash-off from the fleece, incorrect disposal and spillage during administration (Boxall et al., 2002). As with OPs, due to strict regulations, it is thought that the manufacturing process does not contribute greatly to the introduction of MLs into the environment in the European Union or the United States of America (Boxall et al., 2003).

MLs have been identified as having a high possible impact on aquatic and terrestrial organisms (Boxall et al., 2006; Beynon, 2012a). More recently, they have also been observed to have a phytotoxic impact (Eichberg et al., 2016; Vokral et al., 2012). No antialgal, antibacterial, antifungal or antiprotozoal effects of MLs have been observed in the laboratory (Halley et al., 1989a; Escher et al., 2008) and in the field they were found to have no influence on the nitrification and respiration of soils (Halley et al., 1989a; Halley et al., 1989b). However, there is some evidence to suggest that chronic exposure of ivermectin may reduce spore production and germination in the soil fungus *Fusarium oxysporum* and increase spore production in *Phanerochaete chrysosporium* and *Mucor racemosus* (Kollman et al., 2003). There may be other indirect effects on other organisms that prey on ML-affected organisms and on ecosystem services provided by ML-affected organisms, but there is limited evidence available on this.

The failure of ivermectin in treating *P. ovis* in Belgian blue cattle was first reported in 2010 (Lekimme et al., 2010), although it was not determined whether this was due to the development of resistant strains of *P. ovis*. Resistance of *P. ovis* from sheep mites to moxidectin was reported in 2018 (Doherty et al., 2018) and to ivermectin and doramectin in 2019 (Sturgess-Osborne et al., 2019). Currently reports and confirmation of resistance have only been located in Wales, the Welsh borders and the South West of England, however, resistant mites may now be spreading via sheep movements (Sturgess-Osborne et al., 2019).

Macrocyclic lactones (MLs), as well as being used to treat sheep scab, are also used to treat other parasitic diseases in sheep, primarily those caused by endoparasites (Kenyon et al., 2017). Resistance to MLs in gastrointestinal nematodes of sheep has already been widely reported in the UK (Bartley et al., 2003) and worldwide (Kaplan & Vidyashankar,

2012; Keane et al., 2014). The use of MLs to treat one parasitic disease is therefore not only increasing the selection pressure for resistance for that particular disease, but also for others (Kenyon et al., 2017), which is an important issue to take into consideration when using MLs to treat sheep scab.

1.4.5 Potential future treatments

The recent draft genome assembly of *P. ovis* (Burgess et al., 2018) may be useful in future in the development of new chemical control methods for *P. ovis*. However, it is likely that with new chemical controls, there still might be negative effects on the environment as seen with the current chemical treatments.

Attempts to develop a vaccine for sheep scab have been carried out over the past 21 years, initially using mite extracts (Pruett et al., 1998; Smith et al., 2002; Smith & Pettit, 2004) and more recently using a cocktail vaccine with seven targets (Burgess et al., 2016). However, none of the attempts have achieved more than a 55% reduction in mite numbers and lesion size (Burgess et al., 2016). The draft genome assembly of *P. ovis* may also help in future development of the vaccine (Burgess et al., 2018).

Two fungal species, *Metarhizium anisopliae* and *Beauveria bassiana* , have been tested as biological control agents for *P. ovis* mites in a number of attempts to develop an alternative treatment for sheep scab (Smith et al., 2000; Brooks & Wall, 2001; Brooks et al., 2004; Lekimme et al., 2006; Abolins et al., 2007; Lekimme et al., 2008; Jiang et al., 2019). Although success was seen *in vitro,* the reality of applying these treatments *in vivo* makes it an impractical control method, as there is not currently an automated mechanism for applying the material directly to the skin of the sheep, which is necessary for the treatment to have the desired effect (Jiang et al., 2019). In addition, the texture of sheep fleece may limit the spore germination rate of *B.bassiana* (Taylor et al., 2009).

A study found that *Comamonas spp.,* an endosymbiont bacteria in other arthropod species, was also part of the community of bacteria found on *P. ovis* mites (Hall et al., 2015). If it is identified that *Comamonas spp.* is also an endosymbiont of *P. ovis*, then it could be a prospective target for endosymbiont control. The study also found that the *P. ovis* mites exposed to the antibiotics, tetracycline and gentamicin, had reduced survival compared to the control and also reduced bacterial density. However, use of antibiotics to control

sheep scab is not a sustainable method of future control in light of the evolution of antibiotic resistance (Bonhoeffer et al., 1997).

It has been suggested that plant essential oils may be an effective alternative to chemical treatments for arthropod pest management, since they are more easily degraded, have low environmental impact and low toxicity to humans (Park & Tak, 2016). A number of *in vitro* studies have identified essential oils which have a toxic effect on *Psoroptes* mites at specific concentrations (Perrucci et al., 1995; Macchioni et al., 2006; Shang et al., 2019). The most recent of these (Shang et al., 2019) found that out of the 12 compounds tested for acaricidal activity against *Psoroptes cuniculi* mites, eugenol was the most effective. It has been suggested that eugenol toxicity is conferred through regulation of the mRNA expression of glutathione S-transferase, catechinic acid and thioredoxin genes (Ma et al., 2019). It was found that eugenol is safe for both humans and animals at the doses needed for toxicity for the mites (Shang et al., 2019). Other studies have found linalool and trans-cinnamic acid to be effective *in vivo* (Perrucci et al., 1997; Wall & Bates, 2011). However, the short residual period of activity of trans-cinnamic acid (maximum 7 days post-treatment) limits its use in preventative treatment of sheep scab. In addition, for any essential oil to be developed into a useful product, there would need to be advances in efficient and effective application of the product to the skin (Wall & Bates, 2011).

No breed, sex or age predisposition to scab was found in a survey of sheep scab in Ireland (O'Brien, 1992). However, yearling sheep and lowland breeds with wool follicles at high densities may be more susceptible to sheep scab infestation (Bates, 1997b; Fourie et al., 1997). Furthermore, when the mite strain is constant, but the sheep breed is different, natural differences between breeds in terms of skin physiology or fleece microclimate, may result in different clinical outcomes (Smith et al., 2001). Hence, husbandry of specific sheep breeds could contribute to national scab management; however, the stratified sheep husbandry system present in the UK, with specific upland breeds crossed with lowland breeds to produce lambs for market (Tempelman & Cardellino, 2007), makes any reduction in breed diversity an unlikely method of control in the near future.

Recently, Marr et al. (2018) have demonstrated successful RNA interference of three *P. ovis* genes: those which encode Pso o 2 (the Group 2 allergen), μ-class glutathione S-

transferase and β-tubulin. More work needs to be done before this could be developed into a successful future treatment.

1.5 CURRENT STATUS OF SHEEP SCAB IN GREAT BRITAIN

1.5.1 Prevalence and risk

The available data on scab prevalence in Great Britain is limited, since scab is currently only notifiable in Scotland (Scottish Government, 2010) and even with notification, underreporting is likely, since reporting is voluntary and not enforced (DEFRA, 2011). However, there have been a number of surveys over the past 20 years looking at the prevalence of sheep scab across the regions of Great Britain (Table 1.2). Of these, the most recent is for Wales only (Chivers et al., 2018), with the most recent survey covering the whole of Great Britain collecting data prior to 2009 (Rose 2011).

One of the surveys was a face-to-face survey (Cross et al., 2010) while the rest were postal surveys (Table 1.2). Postal surveys have the advantage of being able to reach a wide and large target of the population, although the response rate is thought to be lower than for other survey techniques (Jones et al., 2013). A low response rate can introduce bias into a questionnaire since those that respond may be self-selected volunteers who might have different views to the general population (Brennan & Hoek, 1992). Face-to-face interviews usually produce a higher response rate than postal surveys and allow more complex questions to be explained, however, they require training to avoid bias in the way questions are asked (Jones et al., 2013).

The questions on whether a farmer had had scab varied across all surveys (Table 1.2), both in terms of phrasing and for the period of time that was asked about. All surveys asked if sheep had scab, other than Chivers et al. (2018) who asked if there had been an 'outbreak' of sheep scab. Bisdorff et al. (2006) and Chivers et al. (2018) asked about a one-year period, while Cross et al. (2010) asked about the previous 5 years and Rose (2011) asked about the number of outbreaks they had "in previous years" (with no cut-off year). Retrospective surveys come with the disadvantage of recall bias which can be greater the longer the time between the event and the survey (Althubaiti, 2016). This is a limitation of all the scab surveys mentioned here and particularly the Rose (2011) survey as there is likely to be higher reporting for more recent cases.

Another limitation of all the surveys is that all questioned were farmers involved in some sort of agricultural cooperative society; the surveys of Bisdorff et al. (2006) and Rose

(2011) were sent to farmers from the National Sheep Association, Cross et al. (2010) were questioning farmers at agricultural shows and Chivers et al. (2018) sent surveys to farmers from the Welsh Lamb and Beef Producers Ltd (WLBP). Farmers who are members of such societies may have more of an interest and commitment to sheep welfare and therefore, this may have led an underrepresentation of prevalence reported in this study.

There was little variation between the overall prevalence reported by the surveys that included the whole of Great Britain (Bisdorff survey reported 9% and Rose survey 8.6%), despite these surveys occurring four years apart (Table 1.2). There were some regional differences in prevalence between the two surveys, although Wales, Scotland and Northern England were the three regions with the highest prevalence across both surveys. The similarity between the results could be attributed to the fact that the farmers surveyed by Rose (2011) were a subset of those surveyed by Bisdorff (2006). This may have introduced bias into Rose's data, since the farmers that respond to two questionnaires about scab may be more conscientious or just more concerned about scab. However, these surveys could suggest that scab remained at a fairly stable level across these four years.

While the data for the whole of Great Britain shows a similar prevalence between surveys, the prevalence data for Wales is quite varied, ranging from 15.8% (Chivers et al., 2018) to 36.5% (Cross et al., 2010). However, this is very likely to be due to the differences in the time the surveys were carried out (Cross was asking about a five-year period, while the others were asking about a one-year period). In addition, the randomised response technique used by Cross et al. (2010), is thought to increase the rate of reporting due to the anonymity of the process. This reduces social desirability bias, which is a phenomenon often seen when asking sensitive questions that leads to a lower response rate or a provision of incorrect answers (Warner, 1965). The higher reported cases in the Cross survey could suggest that underreporting occurred in the other surveys for the rest of Great Britain which did not use this technique.

Without scab being notifiable across Great Britain, our estimates of scab prevalence are restricted by the limitations of these survey data. In addition, following the reports of

resistance of *P. ovis* from sheep mites to moxidectin in 2018 (Doherty et al., 2018) and to ivermectin and doramectin in 2019 (Sturgess-Osborne et al., 2019) (section 1.4.4) it is expected that the prevalence of sheep scab is likely to increase in Great Britain in the coming years.

Seasonal variation in the prevalence of sheep scab in Great Britain has been reported, with higher numbers generally seen in winter (Kirkwood, 1986; Bates 1997b; French et al., 1999; O'Brien, 1999). This may be due to longer sheep fleece length and the higher environmental humidity seen in winter which is thought to provide a better micro-climate for *P. ovis* (Downing, 1936; Spence, 1949; ADAS, 2008). The traditional timings of sheep scab treatments (usually in the summer or autumn) may also have contributed to the seasonal prevalence patterns as, after the compulsory summer dip was removed in 1988, there was a higher prevalence of scab in the autumn in the following years (French et al., 1999). The use of insecticides to control the blowfly *Lucilia sericata* in summer may also inadvertently contribute to the suppression of *P. ovis* in the summer months. Moreover, autumn sales increase the risk of buying in sheep with scab and overwintering leads to increased densities of sheep, both of which are thought to increase the risk of sheep scab in winter (French et al., 1999). Furthermore, ewes are in poorer condition when pregnant (which is usually during the winter) and so may be more susceptible to sheep scab during this season.

Risk factors for scab include lack of quarantine for bought-in sheep, poor fencing, having neighbours with scab and the use of common grazing (Rose & Wall, 2012). Rose and Wall (2012) demonstrated that the majority of farms in the UK (>80%) never, or rarely, get scab while a small number of farms experience repeated outbreaks of scab and may act as sources of infection to their neighbours or through markets.

Table 1.2 Comparison of survey results for sheep scab in Great Britain from 2003-2015. The prevalence considered to be the proportion of respondents who reported at least one outbreak of scab in the survey period.

Reference	Survey Type	Survey period	Response number	Response rate (%)	Overall prevalence (%)	Regional results (%) (From highest to lowest prevalence)	Question asked
(Bisdorff et al., 2006)	Retrospective postal survey	March 2003 – February 2004	1067	30.2	9	Wales-17 Scotland-14 Northern England-11 Central England-6 Eastern England-3 South West England-3	"In the last 12 months, have your sheep had scab (Psoroptic mange)?"
(Rose, 2011)	Retrospective postal survey	March 2007-February 2008 and "in previous years"	399	56.4	8.6	Wales - 20.5 Northern England-14.1 Scotland-7.1 South West England-6.4 Eastern England-5.9 Central England-3.3	"Did any of your sheep have sheep scab between March 2007 and February 2008?" "Have you had scab in previous years?"

						South East England-2.4	
(Cross et al., 2010)	Randomised response technique face-to-face survey	2004-2009	588	n/a	n/a	Wales-36.5 (over a longer time period)	"Have you had scab in your flock in the last 5 years?"
(Chivers et al., 2018)	Retrospective postal survey	January 2015-December 2015	972	14	n/a	Wales-15.8	"Have you had an outbreak of sheep scab since 1 January 2015?" (survey was sent out in Feb 2016)

1.6 USE OF MATHEMATICAL MODELS FOR ANIMAL DISEASE

1.6.1 What are mathematical models and how are they useful in disease control?

At a basic level, a model is a theoretical means of demonstrating the behaviour of an object, or a system of objects. In a mathematical model, mathematics is used to define or represent a system more precisely. Seeing as assumptions must be made for any model, no model can perfectly capture a system. However, they can give insight into patterns that may be seen in real-life systems (Keeling & Rohani, 2008).

Mathematical models can be used in epidemiology to increase understanding of disease dynamics and in scenario analysis to predict future outcomes. Where it is experimentally and ethically difficult to look at disease dynamics in the real world, an epidemiological model provides a simulated world where every aspect of transmission is perfectly recorded and where distinct elements can be examined in isolation (Keeling & Rohani, 2008). Models can be used for risk analysis and to guide surveillance before a pathogen has been introduced into a population (Gottwald et al., 2019), in real-time for forecasting current epidemics (known as Outbreak analytics (Polonsky, 2019)) as seen with Ebola in humans (WHO Ebola Response Team, 2014; Camacho et al., 2015), or in hindsight to learn from past cases, such as the a bubonic plague outbreak in 1900 (Dean et al., 2019).

Epidemiological modelling has been carried out for hundreds of years (Graunt, 1662; Bernoulli, 1760; Snow, 1853; Snow, 1855; Farr, 1866; Hamer, 1906; McKendrick, 1914; Ross, 1915; Kermack & McKendrick, 1927; Kermack & McKendrick, 1932)and has been most commonly used for human diseases, followed by livestock diseases, with the fewest studies on plant diseases (Thompson & Brooks-Pollock, 2019). In more recent years, increases in computational power, along with the production of more detailed datasets have made it possible for huge advances in our understanding of epidemics (Thompson & Brooks-Pollock, 2019).

Compartmental models have been the most common approach for epidemiological modelling (Keeling & Rohani, 2008). Other primary methods used include renewal process models (Nouvellet et al., 2018), agent-based modelling (Ballas et al., 2019), statistical modelling (Kelly et al., 2019) and phylodynamic modelling (models which link pathogen sequencing data with models of disease dynamics) (Frost et al., 2015). Mancy

et al. (2017) have reviewed all these methods and provide advice to help with model selection in disease ecology and animal health.

Although epidemiological models can be useful in predicting the spread of disease and recommending the most effective control methods, when applying these methods to the real world, economic and social factors affecting disease control can often have a major impact on what control methods are actually employed (Edwards-Jones, 2006). Therefore, it is often useful to develop models which look at the economics of disease and farmer behaviour and use these alongside epidemiological models to identify control methods that are both feasible and effective.

1.6.2 Modelling software

Disease models can be built in any of a range of programming languages such as *R* (R Core Team, 2019), *Python*, (Python Core Team, 2015), *Matlab*™ , *C*++ (Stroustrup, 2013), *C* or *Fortran* (Keeling & Rohani, 2008). There are packages in *R* which have been developed specifically for developing disease models, such as EpiModel (Jenness et al., 2018), which reduce the time needed to build a disease model.

There are also some disease-modelling-specific software. A review of many publicly available software tools has been undertaken by Heslop et al. (2017). Many of the tools discussed in this paper have the advantage that they enable models to be built more quickly than if they were written from scratch using a programming language, which is particularly useful when wanting to model an emerging disease. They even allow models to be built or adapted by those without experience of using a programming language. However, a disadvantage of this may be that the users may misunderstand what the software is doing or how it should be applied to their work and this can lead to misuse (Heslop et al., 2017). In addition, the software may be limited in some ways which makes them less applicable to certain diseases or scenarios. Another open source modelling software that is used in this thesis, but is not reviewed by Heslop et al. (2017), is the Spatiotemporal Epidemiological Modeler (STEM), which can be used to build and visually display disease transmission models (Douglas et al., 2019).

Although a population model (Wall et al., 1999) and a species distribution model (Rose, 2011) were developed for *P. ovis*, as well as statistical, spatial models of sheep scab prevalence (Chivers et al., 2018), there have been no previous published attempts to develop epidemiological models of sheep scab epidemiology on a national scale.

1.7 AIMS

The overall aim of this thesis was to develop epidemic and economic models for sheep scab in Great Britain that could contribute to better scab management, reducing the sociological, economic and environmental impact of sheep scab. To do this the thesis first aimed to develop an epidemiological model, starting with within-farm transmission and using sensitivity analyses to test the parameterisation of the model (Chapter 2). The thesis then aimed to further expand the model to include between-farm transmission across the whole of Great Britain via neighbour-neighbour contact of farms (Chapter 3). Improvements to the Chapter 2 within-farm model were made and presented in Chapter 4 and these were then used as part of an alternative between-farm model presented in Chapter 5. Finally, the study aimed to use game theory to look at the economic motivations of farmer's preventative treatment choices for sheep scab, taking into account the unknown choices made by a neighbouring farmer (Chapter 6). The work was designed to use scab in the UK as a case study for the application of modelling approaches that could have application to other parasites and other systems worldwide.

Chapter 2

A BASIC MODEL FOR WITHIN-FARM TRANSMISSION OF SHEEP SCAB

SUMMARY

Epidemiological modelling can be used to aid understanding of the dynamics of a disease and help to predict future transmission. A within-farm transmission model for sheep scab is presented here based on the classic SIR model first developed by Kermack and McKendrick (1927) and Ross (1915). A deterministic version of the model is built in R and a stochastic version is built in the Spatial Temporal Epidemiological Modeler software (STEM). The justification for the choices made when developing the within-farm model are given and the limitations of the model are discussed. The general trend of the model output follows that of experimental data by Berriatua et al. (1999) where an index case of scab was introduced into a naïve flock. In both the model and the experimental data, the fraction of the flock infected increases over time, with the majority infected after 100 days. An uncertainty analysis provides confidence in the estimated parameters in the model; sensitivity analysis shows that the transmission rate, β, has the strongest and most significant influence on the model output and therefore might be targeted in future interventions, for example, by reducing stocking density or increasing quarantine.

2.1 INTRODUCTION: THE RATIONALE FOR MODEL TECHNIQUE, DEVELOPMENT AND TESTING CHOICES

Epidemiological modelling can be used to both improve understanding of disease dynamics and to predict future disease outcomes (Keeling & Rohani, 2008). When looking to reduce the national prevalence of sheep scab, modelling the between-farm transmission of sheep scab is likely to be important (this is investigated in Chapters 3 & 5). However, modelling within-farm transmission may still give insight into directions for future intervention strategies. A within-farm transmission model for sheep scab is described in this chapter and can be used as a stand-alone model, however, it also provides a baseline for subsequent models which look at both within-farm and between-farm transmission. There are a large number of process-modelling approaches that are used to model disease (Mancy et al., 2017) and methods for testing disease models (Wu et al., 2013).

An important aspect to consider when modelling sheep scab transmission within a farm is that this can occur both directly and indirectly; directly, via sheep-to-sheep contact, or indirectly, via contact of sheep to viable *P. ovis* mites in the environment (as described in Chapter 1). When modelling interventions for sheep scab on a farm, it is important to incorporate the fact that the main treatments have a residual activity and so not only treat the disease when it is present, but also protect susceptible and infected individuals from new infection for a specified amount of time following treatment use. Diazinon dips give 63 days protection (Kirkwood & Quick, 1981) and injecting long-acting macrocyclic lactones gives 60 (NOAH, 2017).

Another feature unique to sheep scab that must be taken into consideration when deciding on a disease modelling approach is whether it acts more like a micro- or a macro-parasite. Biologically, micro-parasites are considered to be viruses, bacteria, protozoa, prions or other single-celled organisms, while macro-parasites are multi-cellular organisms such as helminths and fluke. However, the distinction as to whether a disease should be modelled as a micro- or macro- parasitic disease is not as clear from a modelling perspective. Models of macro-parasitic disease will usually take the on-host abundance and life cycle of the parasite into account, while in models of micro-parasites, it is assumed that infection can develop from just a few particles and so only the host's infection status is monitored (Keeling & Rohani,

2008). Biologically, sheep scab is caused by a macro-parasite (*P. ovis*). The abundance and life cycle of *P. ovis* may have some impact on the risk of transmission of sheep scab, however, here it was decided to not include these factors, as the impact of life cycle stage on transmission is currently unknown and including this level of detail would over-complicate the model (this will be justified further in 2.5). Therefore, the epidemiological approach described in this chapter is one which is more commonly used for micro-parasites.

In the model described in this chapter, individual hosts (sheep) are modelled as the unit of infection. Different modelling techniques model hosts with varying levels of detail. A computational technique that has been applied in epidemiology is Agent-Based-Modelling (ABM), where, according to a set of rules, hosts with specified characteristics interact with each other and their environment (Tracy et al., 2018). This technique allows for the individual behaviour of each host to be captured. However, it is not usually used to model disease spread across distances as large as the UK, due to the high computational costs of simulation (Mancy et al., 2017). As the model presented in this chapter was designed with expansion (across Great Britain) in mind, it was decided to assume that the behaviour of individuals is homogenous and to use the more traditional and less computationally heavy SIR compartmental model technique, initially developed by Kermack & McKendrick (1927) and based on the work of Ross (1915).

In an SIR model, the discrete count or proportion of hosts in different disease states (for example, "susceptible", "infected" or "recovered") is recorded (Mancy et al., 2017). Hosts move between disease states as determined by coupled ordinary differential equations (ODEs). The output of these models are the ODE solutions at simulation time steps, which demonstrate the transmission dynamics of the disease (Keeling & Rohani, 2008) . The parameters of compartmental models can be estimated using observational or experimental data. If these are not available, then they are estimated based on expert opinion, statistical inference or comparable systems (Keeling & Rohani, 2008; Hooker et al., 2011). The model described in this chapter is a compartmental model, adapted for sheep scab, with parameters estimated using observational and experimental data from the literature.

Compartmental models can be deterministic or stochastic. Deterministic models produce an identical output when given the same input and therefore a deterministic

epidemiological model always has the same number of individuals being infected at the same time steps in a simulation. However, in a stochastic model, the results are different each time the model is run. Stochastic models of disease are more representative of real-world outbreaks, as these may give different outcomes each time they occur, even if the initial conditions are the same. They are particularly useful when the number of infectious individuals is relatively small or when the overall population is small (Keeling & Rohani, 2008). The within-farm model described in this chapter can be run deterministically or stochastically.

Once a modelling technique has been decided, an appropriate modelling software to use for building the model must be chosen. As discussed in Chapter 1, there are a number of different software packages used by epidemiologists to build disease models. In this chapter, R (R Core Team, 2019) and the Spatiotemporal Epidemiological Modeler (STEM) (Douglas et al., 2019) were used. R is an open-source programming language and environment which is generally used for statistical and graphical techniques, however, it also has packages specifically used in epidemiological modelling, for example, the EpiModel R package (Jenness et al., 2018). The Spatiotemporal Epidemiological Modeler (STEM) is a free open-source software project run on *Equinox* (Eclipse) and coded in *Java*, which allows for compartmental disease models on networks to be built and shared (Ford et al., 2006; Douglas et al., 2019). It has a graphical user interface (GUI) which allows the visual display of the changing infection status of network nodes (for example, farms) over time (Doerr et al., 2019). Both R and STEM were used to build the within-farm transmission model described in this chapter and R was used to analyse the results.

Once a model has been developed initially, it is usually recommended that uncertainty analysis (UA), coupled with a sensitivity analysis (SA), are carried out to explore the uncertainty of the model (Saltelli & Annoni, 2010). These two methods are important because parameter values may not always be known with an appropriate level of certainty, owing to deficiency in suitable measuring techniques, errors when making measurements or differences arising from natural variation (Marino et al., 2008). An UA identifies the confidence in model prediction, while a SA investigates the individual contributions of the model inputs to this confidence level (Saltelli et al., 2019). Coupled together, UA and SA can be useful in improving accuracy of parameter estimates by identifying those that would benefit from more data collection (Buhnerkempe et al., 2011) and identifying the key parameters and

times when interventions should be planned for maximum effect (McLeod et al., 2006; Chitnis et al., 2008).

Methods of UA and SA can generally be grouped into local and global methods. Local methods are those which look at the impact of varying an individual parameter on the model output, while global methods will look at the impact of modifying multiple parameters simultaneously (Saltelli & Annoni, 2010). Although local methods are popular (used in 34% papers, n= 280, in a systematic review of UA and SA methods; (Saltelli et al., 2019)), local methods are not thought to be valid when used for nonlinear models (and only 8% of all papers in the review were confirmed to be using linear models). In addition, it has been argued using geometrical techniques that the most popular local method, the one-at-a-time (OAT) approach, is not sufficient for drawing accurate conclusions about the uncertainty in a model (Saltelli & Annoni, 2010) and the authors suggest that interactions between parameters cannot be identified without simultaneous variation of more than one parameter. Global sensitivity analysis (GSA) explores all areas of uncertainty concurrently, therefore allowing for the space of parameter uncertainties to be properly investigated and incorporating all possible interactions (Salteli et al., 2009). However, the OAT approach can be a useful method to start to explore a model and to give some initial insight into the relationship between model input and output (Wu et al., 2013). A local method and a global method were used in the UA and SA of the model presented in this chapter.

A number of GSA methods are used to test infectious disease models and should be chosen based on the purpose of the sensitivity analysis (Wu et al., 2013). The purpose of the sensitivity analysis in this chapter was firstly to assess the uncertainty in the parameter combinations used in the model and then to identify which parameters might be the most important targets when planning interventions for sheep scab. Wu et al, (2013) have shown that the combination of Latin hypercube sampling (LHS) with partial rank correlation coefficient index (PRCC) is a combined technique which is suitable for achieving these goals.

Latin hypercube sampling (LHS) is a Monte Carlo based sampling method developed by Mckay (1979) that requires less samples than simple random sampling while still retaining the same level of accuracy. This is achieved through assigning a probability distribution to each parameter, dividing the intervals in the distribution into an

assigned number of equally probable regions and then (without replacement) sampling each of these intervals. The output delivers a global analysis of parameter space by treating each parameter as a random variable (Stein, 1987; Helton & Davis, 2002). This technique was used in the uncertainty analysis of the model described in this chapter.

For a model with a nonlinear but monotonic trend between model inputs and outputs, a partial rank correlation coefficient (PRCC) is often used to measure the strength of the relationship between each input and output (Marino et al., 2008). This test measures the monotonicity following elimination of the linear effects of all bar one variable (Marino et al., 2008). The values of PRCC vary from 1 to -1; with the sensitivity of the output to the parameter uncertainty specified by the magnitude of the PRCC value and the sign signifying whether the correlation is positive or negative. The significance of the PRCC is shown by the *p*-value. A PRCC value greater than 0.5 in magnitude indicates that the output is sensitive to the input and it is considered to be significant if the *p*-value is less than 0.05 (Pennington, 2015). This technique was used in the sensitivity analysis of the model described in this chapter.

2.2 AIMS

The work presented in this chapter aimed to describe the development of a within-farm transmission model for sheep scab. It then aimed to investigate whether this model could recreate the general pattern of transmission seen within a flock, as described by Berriatua et al. (1999). The development of the within-farm transmission model for sheep scab was based on the rationale outlined above: sheep scab was considered to be a micro-parasitic disease; individual hosts were to be modelled but their behaviour was assumed to be homogenous; the model would be an adaptation of the classic SIR model and would be run deterministically using R and stochastically using STEM. Uncertainty analysis was to be used to measure the confidence in the parameter combinations used in the model and a sensitivity analysis executed to identify which parameters might be the most important targets when planning interventions for sheep scab; uncertainty analysis would be carried out using LHS and a sensitivity analysis using a OAT approach and PRCC.

2.3 METHODS

2.3.1 Software

STEM and R were used to develop and run the models described here. R was also used to prepare data for STEM and to analyse any outputs from STEM. In STEM, the model was written using the model creator (Douglas et al., 2013). In R, the model was written using base R and the model equations were solved using the lsoda() function from the deSolve package (Soetaert et al., 2010).

2.3.2 Model parameters, flowchart and equations

The within-farm sheep scab transmission model is based on the SIR (susceptible-infected- susceptible) compartmental model which is used widely in epidemiology (Kermack & McKendrick, 1927), but adapted for sheep scab. The number of individual sheep in each disease state is tracked. Individuals are able to move between disease states in the directions indicated by the arrows and at the rates represented by symbols in Fig. 2.1. The model parameters are described in Table **2.1**. It is assumed that within a population all individuals are equally likely to come into contact with each other so that complete mixing occurs.

The disease states include susceptible (unexposed to the parasite), infected (infested with at least one *P. ovis* mite), treated (treated with acaricides and protected from infestation for the duration of the treatment's residual activity) or dead (disease mortalities only). Flocks are assumed to be restocked with a number equal to the number of individuals that die from sheep scab, which is simulated by the movement of individuals from the "dead" disease state to the "susceptible" disease state.

A compartment is needed to track individuals in the "dead" state, so that restocking can be delayed, as it may not always occur as soon as an individual has died. However, "dead" is not a true disease state (indicated by the dashed lines, Fig 2.1); rather, these transitions model the restocking deficit. For the model version described here, it is assumed that the host population size remains constant and that there are no natural births and deaths.

Both susceptible and infected sheep can move to the treated compartment, as treatments can be used both preventatively and reactively. A recovered compartment is not included, since it is thought that sheep do not usually "recover" without treatment even if they appear to have no clinical signs. They will usually still be a carrier of the mite for periods of up to two years and are still able to spread the mites which cause the disease to other individuals (Babcock & Black, 1933; O'Brien, 1995). Therefore, a transition is included whereby infected individuals move back to the susceptible compartment after two years (with recovery rate γ, Fig. 2.1.).

Table 2.1. The symbols used to represent parameters in a within-farm SITD (susceptible-infected-treated-dead) sheep scab model. When applicable, the symbols correspond to those in the parameter glossary in Keeling and Rohani (2008).

Symbol	Meaning
S, I, D, T	Absolute numbers of susceptible (S), infected (I), dead (D) (from disease) and treated (T) individuals
N	The total number of individuals in all disease states
γ	Recovery rate. $\frac{1}{\gamma}$ is the period of infection
m	Disease-induced mortality rate
P	Probability of dying from infection
β	Transmission rate of infection
R_0	Basic reproductive ratio
R(∞)	Final epidemic size
Ψ	Protection rate
θ	Protection loss rate
ξ	Restocking rate

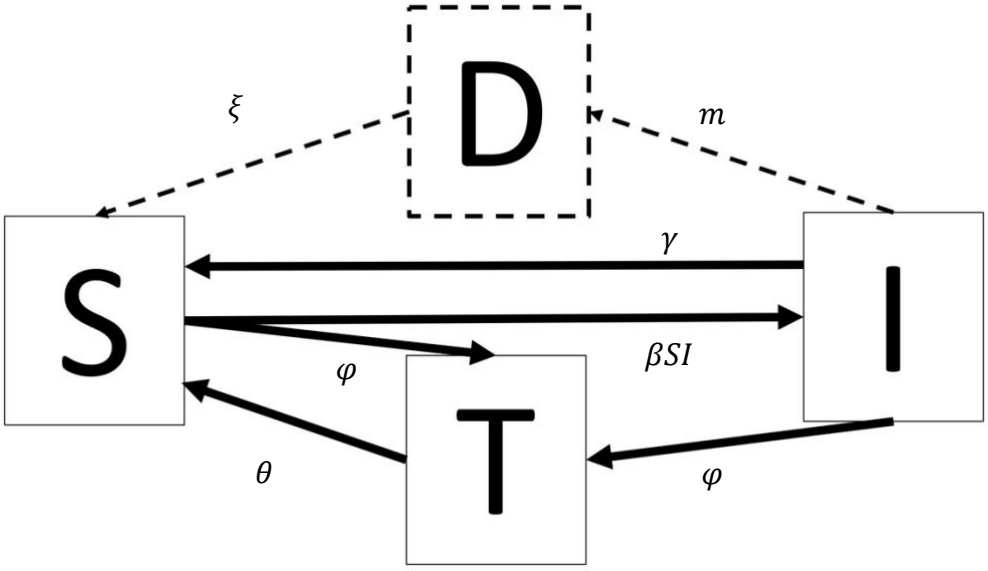

Fig. 2.1. SITD model for sheep scab based on the SIR disease compartment model developed by Kermack & McKendrick (1927). "S" is a compartment for susceptible sheep in a farm, "I" is for sheep infested with at least one *P.ovis* mite, "T" is a compartment for treated sheep (those that have been treated for scab with a product that has residual activity) and "D" is for sheep that have died from scab. The D compartment is included for convenience so that the farm re-stocks to its original size but is not a true compartment of the model (indicated by the dashed lines). It is assumed that the birth rate is equal to the natural death rate. The Greek symbols (defined in Table 2.1) represent the rates at which individuals move between compartments and the arrows indicate the direction of movement.

Individual sheep on a farm move from one compartment to the other as described by the deterministic differential equations 1-4 describing the rate of change of the number of sheep in each disease state over (continuous) time:

$$\frac{dS}{dt} = \gamma I + \xi D + \theta T - \beta SI - \Psi S \quad 2.1.$$

$$\frac{dI}{dt} = \beta SI - \gamma I - mI - \Psi I \quad 2.2.$$

$$\frac{dD}{dt} = mI - \xi D \quad 2.3.$$

$$\frac{dT}{dt} = \Psi(I + S) - \theta T \quad 2.4.$$

where the parameters given are described in **Table 2.1**.

2.3.2.1 Frequency and density dependency

The "transmission term" can be defined as the rate at which susceptible individuals in a population become infected individuals via contact with infectious material (Begon et al., 2002). However, there has been some inconsistency in the use of the transmission term in compartmental models in epidemiology. The area occupied by the whole population, the number of infected individuals and their density within the population, all influence the probability of transmission between susceptible and infectious individuals within a population. Here, frequency- and density-dependency will be described in accordance with the definitions given by Begon et al., 2002.

The transmission rate (β) for the model described here was estimated using data from Berriatua et al. (1999). In this study, using a within-flock sheep scab transmission experiment, 34 out of 40 scab-naïve sheep became infected following the introduction of an infected sheep into a flock (Berriatua et al., 1999). They suggested that susceptible sheep had become infested with scab via host-host contact as well as via contact with viable mites in the environment, as is usual for sheep scab transmission (ADAS, 2008). At higher stocking densities, as well as there being an increased chance of contact between sheep, there will also be an increased risk of contact between a sheep and mites in the environment.

For that reason, it is assumed that the sheep scab transmission is density-dependent, hence the transmission term:

$$FOI = \beta S \frac{I}{A} \qquad 2.5.$$

where A is area, FOI is the force of infection (rate at which each susceptible individual becomes infected (Muench, 1934)) and all other parameters are as specified in Table 2.1.

In all versions of the model described in this thesis, it is assumed that the area is constant on each farm over time and therefore that A = 1 (Begon et al., 2002). Therefore, the transmission term is written as βSI.

2.3.3 Parameter estimation

The units in STEM are the inverse of time, days^{-1}, so all parameters here are calculated as rates per day. Although transmission can occur directly (host-to-host contact) or indirectly (host-to-environmental contact), these are not distinguished between in the model, but are instead included as one factor when estimating parameters. This is because no distinction is made between these parameters in the data that were used to estimate the transmission rate (Berriatua et al., 1999).

2.3.3.1 Recovery rate (γ)

The recovery rate γ can be shown (mathematically) to be:

$$\gamma = \frac{1}{period\ of\ infection} \qquad 2.6$$

assuming a constant recovery rate or an exponentially-distributed infectious period.

It has been suggested that the period of infection for sheep scab without treatment may be to be up to two years (O'Brien, 1995), or at least two years (Babcock & Black, 1933). Although clinical signs might not be present on an infected individual for the whole two-year period, mites can remain concealed within cryptic sites on a sheep,

such as hidden skin folds or the ear (Babcock & Black, 1933; Bates, 1997a). Since one pregnant female mite, if passed to another host, will establish an infection on that host (van den Broek & Huntley, 2003b), it follows that sheep with mites in cryptic sites are may potentially cause infection in another sheep and therefore should be considered to be infected.

Considering all this, the average period of infection will be estimated to be two years (730 days) and therefore the baseline value for the recovery rate is $\frac{1}{730}$ days^{-1}.

2.3.3.2 Disease -induced mortality rate (m)

The disease- induced mortality rate m, is calculated using equation 2.7:

$$m = \frac{\rho}{1-\rho}(\gamma + \mu) \qquad 2.7.$$

where p is the probability that an infected individual dies from infection before either recovering or dying from natural causes, γ is the recovery rate and μ is the natural per capita death rate (Keeling & Rohani, 2008).

It has been estimated that one third of sheep with scab left untreated will die (Babcock & Black, 1933; O'Brien, 1995). Using data provided by APHA on the reported sheep scab outbreaks per county in Great Britain from 2003-2016, it was estimated that 28.23% of submissions of scab cases were reporting deaths. The APHA data is limited since scab was not notifiable in 2003-2016 and so all the reports are voluntary, meaning that not all cases will have been recorded. Farmers or vets may have reported cases to private laboratories, if the location or price for testing were more convenient and so these cases would not be included in the APHA data, as well as those cases that were not tested at all. This may affect the estimate of the mortality rate since milder cases of scab may not have been detected or reported which could mean that 28.23% is an overestimate of the mortality rate. On the other hand, since it is a legal requirement for infected flocks to be treated (MAFF, 1997), the majority of scab cases reported in the APHA data which were not deaths will have been sheep that have been treated for scab and so there may have been unreported mortalities. It is also unknown how many of the reported live individuals would have recovered if left untreated and so 28.23% is likely to be an underestimate

for the disease-induced mortality rate, *m*. Therefore, the higher figure of one third (Babcock & Black, 1933; O'Brien, 1995) was used for *p*:

$$m = \frac{\frac{1}{3}}{1 - \frac{1}{3}}\left(\frac{1}{730} + 0\right)$$

$$m = \frac{1}{1460}$$

2.3.3.3 Transmission rate (β) and R0

2.3.3.3.1 The Berriatua et al., (1999) study

Experimental data from a study by Berriatua et al. (1999) is used to calculate the transmission rate and is used in section 2.3.5.1 as a comparison for the model output. This was a prospective study which tracked the infectious status of susceptible sheep after introduction of an index case of scab. There were five repeats of the experiment: Trials 1A, 1B, 2A, 2B and 2C, each with a range of susceptible sheep from 6 – 20 per group. Trials 1A and 1B originated from a single trial, Trial 1, which was aborted as the scab index case had to be removed for welfare reasons. The group of sheep from Trial 1 were split into two groups and a new index case was introduced into Trial 1A, while a single secondary infested sheep from Trial 1 became the index case in Trial 1B. In Trial 1, one sheep had lesions and was classed as infected after 10 days, but then showed no lesions the following week and so was classed again as susceptible (as sheep cannot be considered to be 'recovered' from scab - Babcock & Black, 1933; O'Brien, 1995). Information about each trial is provided in Table 2.2 including the number of sheep in each experiment and the final size.

Table 2.2 Details of 6 experimental trials in a prospective study which tracked the infectious status of susceptible sheep after introduction of an index case of scab (Berriatua et al., 1999).

Trial number	Dates of trial	Length of trial	Number of susceptible sheep	Stocking density	Final size	Final size fraction infected	Time to first cases
1 (split into Trial 1A and 1B on week 8)	9th October 1996 to 10th January 1997	14 weeks (includes trial 1A and 1B)	21 (one susceptible sheep became infected and became susceptible again so is counted twice)	21 sheep/50m^2 ~420 sheep/ 1000m^2	n/a	n/a	1 week- 2 cases
1A	4th December 1996-10th January 1997	6 weeks	10	11 sheep/38m^2 ~289 sheep/1000 m^2	10	1	1 week- 1 case
1B	4th December 1996-10th January 1997	6 weeks	9	10 sheep/34m^2 ~294 sheep/ 1000m^2	3	3/9	2 weeks- 2 cases
2A	6th February 1997 to 23rd April 1997	12 weeks	6	7 sheep/20m^2 ~350 sheep/ 1000m^2	6	1	2 weeks- 3 cases
2B	6th February 1997 to 23rd April 1997	12 weeks	6	7 sheep/20m^2 ~350 sheep/ 1000m^2	6	1	3 weeks- 3 cases
2C	6th February 1997 to 23rd April 1997	12 weeks	6	7 sheep/20m^2 ~350 sheep/ 1000m^2	6	1	7 weeks- 2 new cases

2.3.3.3.2 Calculation of transmission rate

As mentioned in the introduction, sheep scab can be transmitted directly via sheep-to-sheep contact and indirectly via contact with mites in the environment. However, the transmission rate is estimated using data from a study where the mode of transmission was not determined (Berriatua et al., 1999). Therefore, determination between these two modes of transmission is not used in the model and so the transmission parameter includes the impact of both direct and indirect transmission.

The transmission rate, β, per individual can be calculated by rearranging the equation for R_0:

$$R_0 = \frac{\beta}{\gamma + m} \qquad 2.8.$$

Where R_0 is the "number of secondary infectives per index case in a naïve population of susceptibles" (Keeling & Rohani, 2008). All other parameter symbols match those already defined in Table 2.1. Since a constant birth and death rate is assumed, these are not included in the equation. It is also assumed that mortality can occur at any time point during infection.

This equation can be rearranged to make β the subject:

$$\beta = R_0(\gamma + m) \qquad 2.9.$$

The values of γ and *m* have already been described in sections 2.3.3.1 and 2.3.3.2 respectively. R_0 can be estimated using Fig. 2.2. (taken from Keeling & Rohani, 2008), equation 2.10 and data from Berriatua et al. (1999).

In the Berriatua et al (1999) study, 34 out of 40 (proportion- 0.85) scab-naïve sheep became infected following the introduction of an infected sheep suggesting a basic reproductive ratio (R_0) of 2.24 (Fig 2.2). This can also be solved numerically using guidance and the following equation from Keeling and Rohani (2008):

$$1 - R(\infty) - S(0)e^{e^{-R(\infty)R_0}} = 0 \qquad 2.10.$$

Assuming that the entire population is susceptible, then S(0) = 1. The final proportion of recovered individuals, or the total proportion of the population that gets infected (so in this case 0.85) is R(∞).

Substitute these values in and rearrange to get:

$$0.15 = e^{-0.85R_0}$$

Log both sides of the equation to get:

$$\ln 0.15 = -0.85R_0$$

Rearrange:

$$\frac{\ln 0.15}{-0.85} = R_0$$

$$R_0 = 2.232\ (3dp)$$

This value of R_0 is very similar to the value of 2.24 obtained by looking visually at Fig 2.2, but the more accurate result, 2.23 will be used.

Therefore:

$$\beta = 2.23 * (\frac{1}{730} + \frac{1}{1460})$$

$$\beta = \frac{669}{146000}$$

β is the risk of transmission from an infected sheep to a susceptible sheep per day (assuming homogenous mixing). With this value of β, in a flock of 100 sheep, where 1 is infected and 99 are susceptible, it would take an average of 2 days for an infected sheep to generate a second infected sheep (this is calculated using $\frac{1}{\beta \times S}$).

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Fig. 2.2. The final fraction of a population which is infected as a function of the basic reproduction ratio, R_0. This is Fig. 2.2 from Keeling and Rohani (2008) with dashed line added to show the reading for R_0 when the fraction of the flock infected is 0.85, as seen in experiments by Berriatua et al. (1999). The curve can be obtained by solving equation 9 (Keeling & Rohani, 2008) using the Newton-Raphson method. It is assumed that the entire population is susceptible, S(0)=1 and therefore that the greatest epidemic size is produced.

2.3.3.4 Protection rate (ψ) and protection loss rate (θ)

The protection rate, ψ, and the protection loss rate, θ, are set according to the timings of any interventions that occur. If the protection rate is set to zero, then no individuals are treated (moved from the "S" and "I" compartments to the "T" compartment); if it is set to one, then all are treated. Other proportions in between zero and one can be used to indicate proportions of the flock being treated, or the efficacy of a treatment. If the protection loss rate is set to zero, then all treated individuals remain protected from sheep scab; if it is set to one, then all become susceptible again.

These parameters can be modified at different time steps to simulate the use of control methods. Once the protection rate has been modified and individuals have moved to the "T" (treated) compartment, then the number of time steps before the protection loss rate is modified can be specified, to simulate the residual activity of acaricides, which for the organophosphate acaricide Diazinon, is reported to be 63 days (Kirkwood & Quick, 1981) and 60 days for the long-acting injectable formulation of the macrocyclic lactone Moxidectin (National Office of Animal Heath, 2017).

The application of the protection and protection loss rates in STEM is unconventional and is described in more detail in the Appendix of the thesis.

2.3.3.5 Restocking rate

The restocking rate, ξ, has a default value of 1 (due to the assumption that the flock size is constant). This means that all individuals who die from infection and move to the "D" compartment are continuously replaced by susceptible individuals in the flock. This assumes that farmers will instantly replace any individuals lost to sheep scab.

If replacement is not used, then the value should be 0. If a slower rate of replacement is required, then values between 0 and 1 can be used.

2.3.4 Stochasticity

The model described in this chapter can be deterministic or stochastic. Equations 2.1-2.4 can be solved deterministically using solvers for ordinary differential equations (ODEs) such as the lsoda() function in R from the deSolve package (Soetaert et al., 2010).

When running the model in STEM, as well as having the option to use ODE solvers, it is also possible to solve equations 2.1-2.4 stochastically by adding noise to the deterministic result. This works by using the deterministic result at each transition (transitionCount) to draw a new value for the transition (iTransitionCount) (always an integer) from a discrete binomial distribution (provided by the Apache Commons math ™ library) (Kaufman et al., 2019a) using the number of individuals at the source compartment (sourceCount). The result is used as the new value for the transition (iTransitionCount) and is subtracted from the source compartment (sourceCount) and added to the destination compartment (targetCount). This is shown in this extract of STEM source code taken from org.eclipse.stem.solvers.stochastic.impl.StandardStochasticImpl.java:

```
// Do departures. The stochastic solver will make sure the source
// and the target are both updated with the same stochastic value

for(Exchange departureExchange:iLabDeltaVal.getDepartures()) {
    ExchangeType type = departureExchange.getType();
    double transitionCount = departureExchange.getCount();
    double sourceCount=0.0, targetCount=0.0;
    switch(type.getValue()) {
        case ExchangeType.COMPARTMENT_TRANSITION_VALUE:

            sourceCount = iLabCurrentValue.eGetDouble(departureExchange.getSource().getFeatureID());
            targetCount = iLabCurrentValue.eGetDouble(departureExchange.getTarget().getFeatureID());

            // We cannot move people that does not exist
            if(sourceCount > 0) {
                // Draw stochastic count
                double draw = transitionCount/sourceCount;
                if(draw > 1.0) draw = 1.0;
                int iTransitionCount = binomialDist.fastPickFromBinomialDist(draw, (int)Math.round(sourceCount));
                if(sourceCount < iTransitionCount)
                    iTransitionCount = (int)Math.floor(sourceCount); // Move everyone, but if it's less than 1 person move 0
                // Update the source and the target
                iLabCurrentValue.eSetDouble(departureExchange.getSource().getFeatureID(), sourceCount - iTransitionCount);
                iLabCurrentValue.eSetDouble(departureExchange.getTarget().getFeatureID(), targetCount + iTransitionCount);
                // Add to incidence(s).
                if(departureExchange.getForIncidence() != null)
                    for(EAttribute ea:departureExchange.getForIncidence())
                        iLabCurrentValue.eSetDouble(ea.getFeatureID(),
                            iLabCurrentValue.eGetDouble(ea.getFeatureID())+iTransitionCount);

            } // else nothing to do.
```

2.3.5 Model Testing

The model described in this chapter is tested in three ways: first, by comparing model results with the estimated parameters calculated in section 2.3.3 to real data, then by running an uncertainty and a sensitivity analysis on the main parameters β, γ, m, and ξ.

2.3.5.1 Comparison of simulation results from one farm to real data

A simulation of the model was run where one sheep was infected initially (day 0) and there were eight susceptible sheep. This was the average number of susceptible sheep used in the experiments done by Berriatua et al. (1999) and in all Berriatua experiments, only one infected sheep was introduced to a susceptible group. The time period of the simulation was 100 days, as the maximum number of days in the experiments was 98. It was assumed that the birth and death rate are equal. All parameters used are as calculated in section 2.3.3. No control measures were used.

The simulation was run deterministically in R and the equations solved numerically using the lsoda() function as part of the deSolve package (Soetaert et al., 2010) in R. The simulation was also run multiple times stochastically (n=500) in STEM.

These results are compared visually with the results from five trials (Groups 1A, 1B, 2A, 2B and 2C) in the study by Berriatua et al. (1999) (Fig. 2.3, Fig. 2.4). The output compared is the prevalence of infection at the end of each week (the total number of infected sheep in the flock on the final day of each week). The expected data were the median infected count at the end of each week across all five Berriatua experiments. A Pearson's Chi-squared test for count data was carried out using the "chisq.test" function from the "stats" (v3.6.1) package in R in order to test the null hypothesis that the model data and the experimental data from the Berriatua experiment were from the same distribution. This was assumed to be the case where the p value was greater than 0.01. The p value was calculated from the asymptotic chi-squared distribution of the test statistic.

2.3.5.2 Uncertainty and sensitivity analyses

The UA and SA were both run with respect to the output of most interest in this model, as suggested by Salteli et al. (2009), which in this case was the number of sheep infected on a farm as a function of time (I(t)).

For the UA, LHS was used to generate 100 random parameter combinations to be used in the model for four parameters: transmission rate (β), recovery rate (γ), disease-induced mortality rate (m) and the restocking rate (ξ). This was done in R using the randomLHS() function from the "lhs" package (Carnell, 2019) (correlations between parameters were not included). R_0 was also calculated for each parameter combination using equation 2.8. The probability density function (PDF) was assumed to be uniform for all parameters. The PDF range has been reported to be more influential in UA or SA results than the PDF distribution (Iman & Helton, 1988; Campolongo et al., 2000) and so it was thought that it would be useful to examine results from a number of different PDF ranges. Latin hypercube sampling was carried out three times, to allow for different PDF ranges to be used. For the transmission rate (β), recovery rate (γ) and disease-induced mortality rate (*m*), the PDF range was 10% above and below the baseline parameter value in the first LHS, 50% in the second and 100% in the third. As the baseline value for the restocking rate (ξ) was the maximum value possible for the restocking rate (ξ=1), it was decided that the PDF range for all three iterations of LHS would be from 0 to 1 so that only parameter values of interest were explored (<1) and a wide range of values were investigated, particularly as ξ was not estimated using data from the literature. For each of the three LHS iterations, the model was run in R deterministically 100 times, once for each group of generated parameters. Each simulation was run for 100 time steps (simulated days).

To identify which correlation test for the sensitivity analysis would be most suitable, the relationship between each parameter of interest and the output (to test for monotonicity) was investigated, by running simulations of the R deterministic model, using the baseline values for all parameters except the parameter of interest, which was varied from 0 to 1 by 0.001 (a OAT approach). The specific output that was investigated was the fraction of the flock infected at time step 100 when a single sheep was infected and 8 sheep were susceptible at time step 0. This was carried out for all four parameters used in the LHS (β, γ, m and ξ) and for 100 time steps.

The partial rank correlation coefficient (PRCC) was selected as the most suitable correlation test to further investigate the relationship between the model inputs and outputs (Marino et al., 2008) using the results from the LHS for the results where the PDF ranges are 100% above and below the baseline values for β, γ and m and the PDF range for ξ is 0 to 1. The PRCCs between each of β, γ, m and ξ and the fraction of infected sheep at time step 100 were calculated using the pcc() function from the sensitivity package (Ioss et al., 2018) with one thousand bootstrap replicates and a 0.95 confidence level of the bootstrap confidence intervals. The PRCCs were also calculated using the epi.prcc() function from the "epiR" package (Stevenson et al., 2018) with a two-sided test, as this function also calculates the p-value for each of the test statistics of the significance that the PRCC is greater than or less than zero.

2.4 RESULTS

2.4.1 Comparison of simulation results from one farm to real data

In the stochastic runs (n=500) of the SITD model for one farm, the median fraction of sheep infected at day 100 was 0.78 (2dp) (above the 97.5th percentile = 1, upper quartile = 0.89 (2dp), lower quartile = 0.56 (2dp), below the 2.5th percentile = 0). The fraction of sheep infected at day 100 in the R deterministic model was 0.81. In the results from Berriatua et al. (1999), on day 100 of each trial, the median fraction of sheep infected was 1 (above the 97.5th percentile = 1, upper quartile = 1, lower quartile = 1, below the 2.5th percentile = 0.46). The raw data from Trials 1A, 1B, 2A, 2B, and 2C from Berriatua et al. (1999) are plotted with the results from the stochastic and deterministic runs of the model (Fig. 2.3), while the median, interquartile range and 2.5-97.5 percentiles of all five Berrituata trials is plotted with the same model simulation results on a separate figure (Fig. 2.4).

The null hypothesis that the model output and the experimental data were from the same distribution was rejected for both the deterministic (χ^2= 51.458, df = 14, p < 0.001) and stochastic (χ^2= 60.537, df = 14, p < 0.001) models. However, there is some overlap between the confidence intervals of the stochastic output and the experimental data (Fig. 2.3, Fig. 2.4).

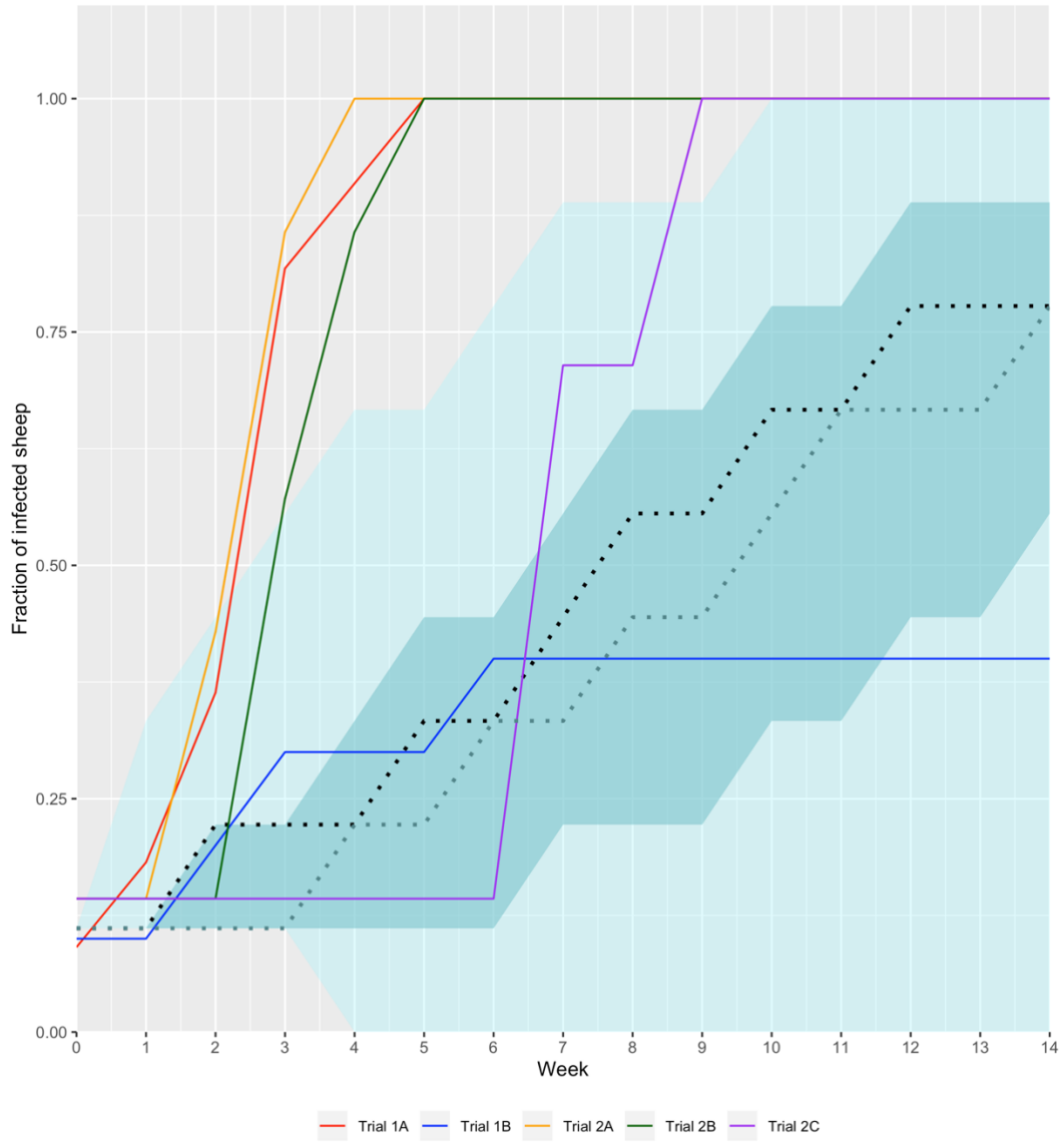


Fig. 2.3. Fraction of flock infected with sheep scab over a period of 14 weeks in experimental data and in model simulations after introduction of one index case of scab. The results are given as integers of sheep per week (hence the step-like nature) and indicate the number of infected sheep at the end of each week divided by the number of sheep in the flock (the end-of-week prevalence). The unbroken lines are the results from five trials described in the Berriatua et al. (1999) paper: with the associated colours indicated in the legend. The dashed lines are results from the model simulations; the black line is the rounded deterministic result (from the R model) and the dashed, blue line is the median stochastic result (n= 500, from STEM). The darker shaded area is the interquartile range of the stochastic results and the lighter shaded area is the 2.5-97.5th percentile range of the stochastic results. In the simulations, there was one infected sheep and eight susceptible sheep on day 0. In the experimental data, there was one infected sheep and a range of 6-10 susceptible sheep on day 0.

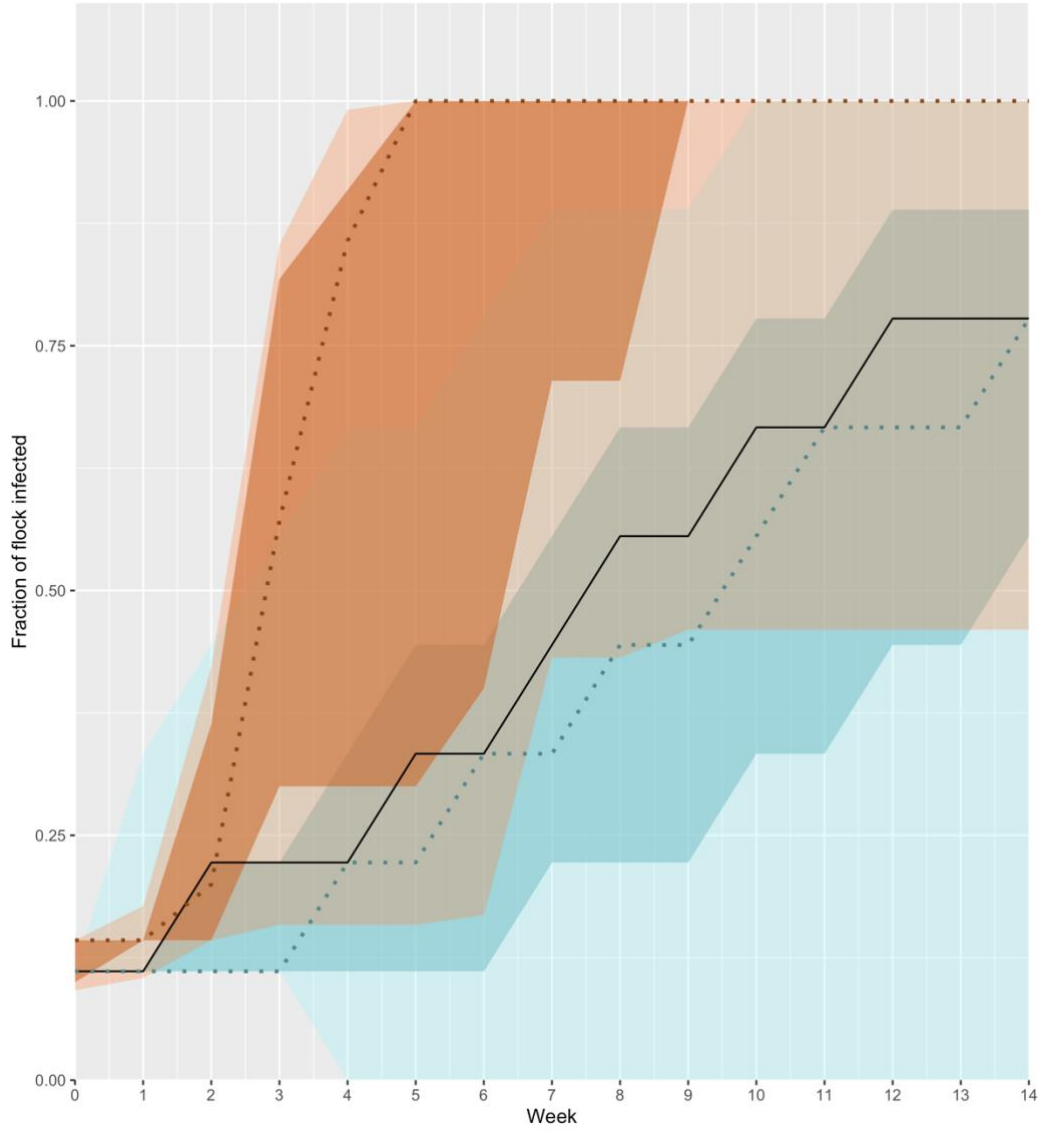


Fig. 2.4. Fraction of flock infected with sheep scab over a period of 14 weeks in summarised experimental data and in model simulations after introduction of one index case of scab. The results are given as integers of sheep per week (hence the step-like nature of the graph) and indicate the number of infected sheep at the end of each week divided by the number of sheep in the flock (the end-of-week prevalence). Results from trials 1A, 1B, 2A, 2B and 2C in the Berriatua et al. (1999) study were summarised (blue), as were the results from 500 runs of the stochastic version of the within-farm SITD model of sheep scab (orange). The darker shaded areas indicate the upper and lower quartiles, the lighter shaded areas the 2.5th and 97.5th percentiles and the dashed, coloured lines show the median. The black line is the result from the deterministic version of the model. In the simulations, there was one infected sheep and eight susceptible sheep on day 0. In the experimental data, there was one infected sheep and a range of 6-10 susceptible sheep on day 0.

2.4.2 Uncertainty and Sensitivity analysis of parameters

2.4.2.1 Latin hypercube sampling

A summary of the parameter values selected in three iterations of LHS is given, where a PDF range 10% (Table 2.3a), 50% (Table 2.3b) and 100% (Table 2.3c) above and below the baseline parameter values for β, γ and m were used and a PDF range of 0 to 1 was used for ξ. For the iteration with PDF range 10%, no values of R_0 were below 1 or above 5, for the 50% PDF range, 2% of R_0 values were below 1 and 2% were above 5 and for the 100% PDF range, 23% of R_0 values were below 1 and 21% were above 5.

Table 2.3. Summary data (n=100) for parameter combinations calculated using LHS in an uncertainty analysis of a within-farm SITD transmission model of sheep scab. Four parameters were investigated: transmission rate, β, recovery rate, γ, disease-induced mortality rate, *m* and the restocking rate, ξ) and the corresponding R_0 values are given (to 3 decimal places) The range of the probability distribution was 10% above and below the baseline parameter values for β, γ and *m* in (**a),** 50% in (**b)** and 100% in **(c).** For all three tables, the range of the probability distribution was from 0 to 1 for ξ. The values for β and ξ are rounded to two significant figures and the values for γ and *m* are given as fractions with a numerator of 1 and the denominator rounded to the nearest whole number. This is to allow for a clearer interpretation of γ and *m* where the denominator gives the number of days before recovery (γ) or mortality (*m*). All units are day^{-1} other than for R_0 which has no units.

(a)

	β	γ	*m*	ξ	R_0
Baseline value in model	4.6×10^{-3}	$\frac{1}{730}$	$\frac{1}{1460}$	1	2.232
Minimum value	4.1×10^{-3}	$\frac{1}{810}$	$\frac{1}{1613}$	8.3×10^{-3}	1.882
1st Quartile	4.4×10^{-3}	$\frac{1}{769}$	$\frac{1}{1534}$	2.5×10^{-1}	2.112
Median	4.6×10^{-3}	$\frac{1}{730}$	$\frac{1}{1460}$	5.0×10^{-1}	2.210
Mean	4.6×10^{-3}	$\frac{1}{730}$	$\frac{1}{1460}$	5.0×10^{-1}	2.234
3rd Quartile	4.8×10^{-3}	$\frac{1}{695}$	$\frac{1}{1389}$	7.5×10^{-1}	2.337
Max	5.0×10^{-3}	$\frac{1}{664}$	$\frac{1}{1333}$	9.9×10^{-1}	2.630

(b)

	β	γ	m	ξ	R_0
Baseline value in model	4.6×10^{-3}	$\frac{1}{730}$	$\frac{1}{1460}$	1	2.232
Minimum value	2.3×10^{-3}	$\frac{1}{1429}$	$\frac{1}{2941}$	9.8×10^{-4}	0.943
1st Quartile	3.4×10^{-3}	$\frac{1}{962}$	$\frac{1}{1961}$	2.5×10^{-1}	1.619
Median	4.6×10^{-3}	$\frac{1}{730}$	$\frac{1}{1449}$	5.0×10^{-1}	2.280
Mean	4.6×10^{-3}	$\frac{1}{730}$	$\frac{1}{1471}$	5.0×10^{-1}	2.360
3rd Quartile	5.7×10^{-3}	$\frac{1}{585}$	$\frac{1}{1176}$	7.5×10^{-1}	2.926
Max	6.8×10^{-3}	$\frac{1}{488}$	$\frac{1}{1000}$	9.9×10^{-1}	5.584

(c)

	β	γ	m	ξ	R_0
Baseline value in model	4.6×10^{-3}	$\frac{1}{730}$	$\frac{1}{1460}$	1	2.232
Minimum value	1.74×10^{-6}	$\frac{1}{111111}$	$\frac{1}{294118}$	1.2×10^{-3}	0.001
1st Quartile	2.3×10^{-3}	$\frac{1}{1449}$	$\frac{1}{2941}$	2.5×10^{-1}	1.139
Median	4.6×10^{-3}	$\frac{1}{730}$	$\frac{1}{1449}$	5.0×10^{-1}	2.444
Mean	4.6×10^{-3}	$\frac{1}{730}$	$\frac{1}{1470}$	5.0×10^{-1}	3.614
3rd Quartile	6.9×10^{-3}	$\frac{1}{490}$	$\frac{1}{978}$	7.5×10^{-1}	3.804
Max	9.1×10^{-3}	$\frac{1}{368}$	$\frac{1}{735}$	1	27.659

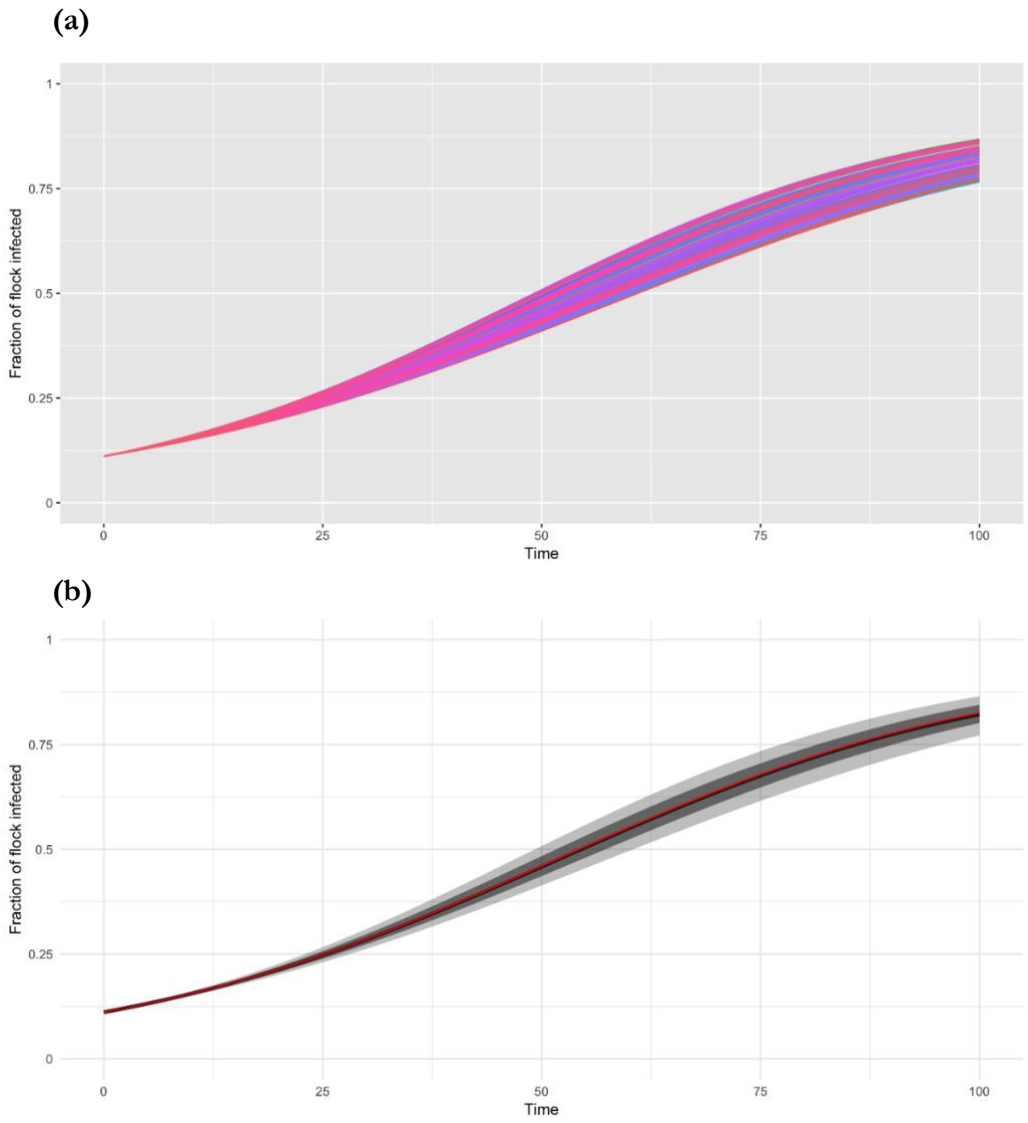


Fig. 2.5. Latin Hypercube Sampling Sensitivity Analysis of the transmission rate (β), recovery rate(γ), disease-induced mortality rate (*m*) and the restocking rate (ξ) in a deterministic version of a within-farm SITD model of sheep scab. The PDF range was 10% above and below the baseline parameter values for β, γ and *m* and from 0 to 1 for ξ. At time step one, 1/9 sheep is infected. The PDF distribution was uniform for all parameters. (a) The fraction of flock infected over 100 time steps is are given for 100 parameter combinations (N=100). (b) The results are summarised, showing the median result (black line), interquartile ranges (dark grey shading) and 97.5th and 2.5th percentiles (light grey shading). The red line in (b) indicates the result from the R deterministic run of the model under the baseline parameters specified in section 2.3.3.

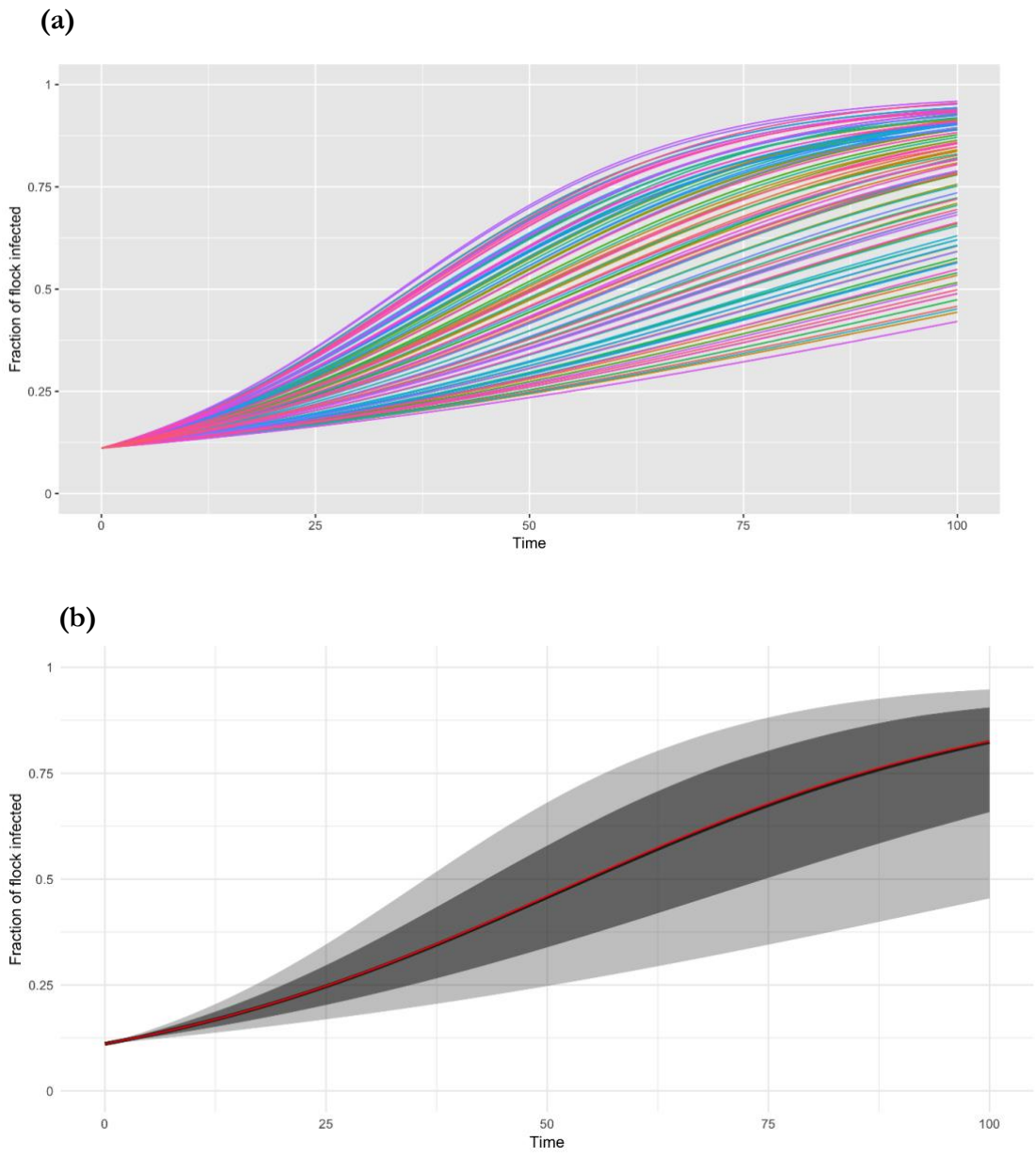


Fig. 2.6. Latin Hypercube Sampling Sensitivity Analysis of the transmission rate (β), recovery rate(γ), disease-induced mortality rate (*m*) and the restocking rate (ξ) in a deterministic version of a within-farm SITD model of sheep scab. The PDF range was 50% above and below the baseline parameter values for β, γ and *m* and from 0 to 1 for ξ. At time step one, 1/9 sheep is infected. The PDF distribution was uniform for all parameters. (a) The fraction of flock infected over 100 time steps is are given for 100 parameter combinations (N=100). (b) The results are summarised, showing the median result (black line), interquartile ranges (dark grey shading) and 97.5th and 2.5th percentiles (light grey shading). The red line in (b) indicates the result from the R deterministic run of the model under the baseline parameters specified in section 2.3.3.

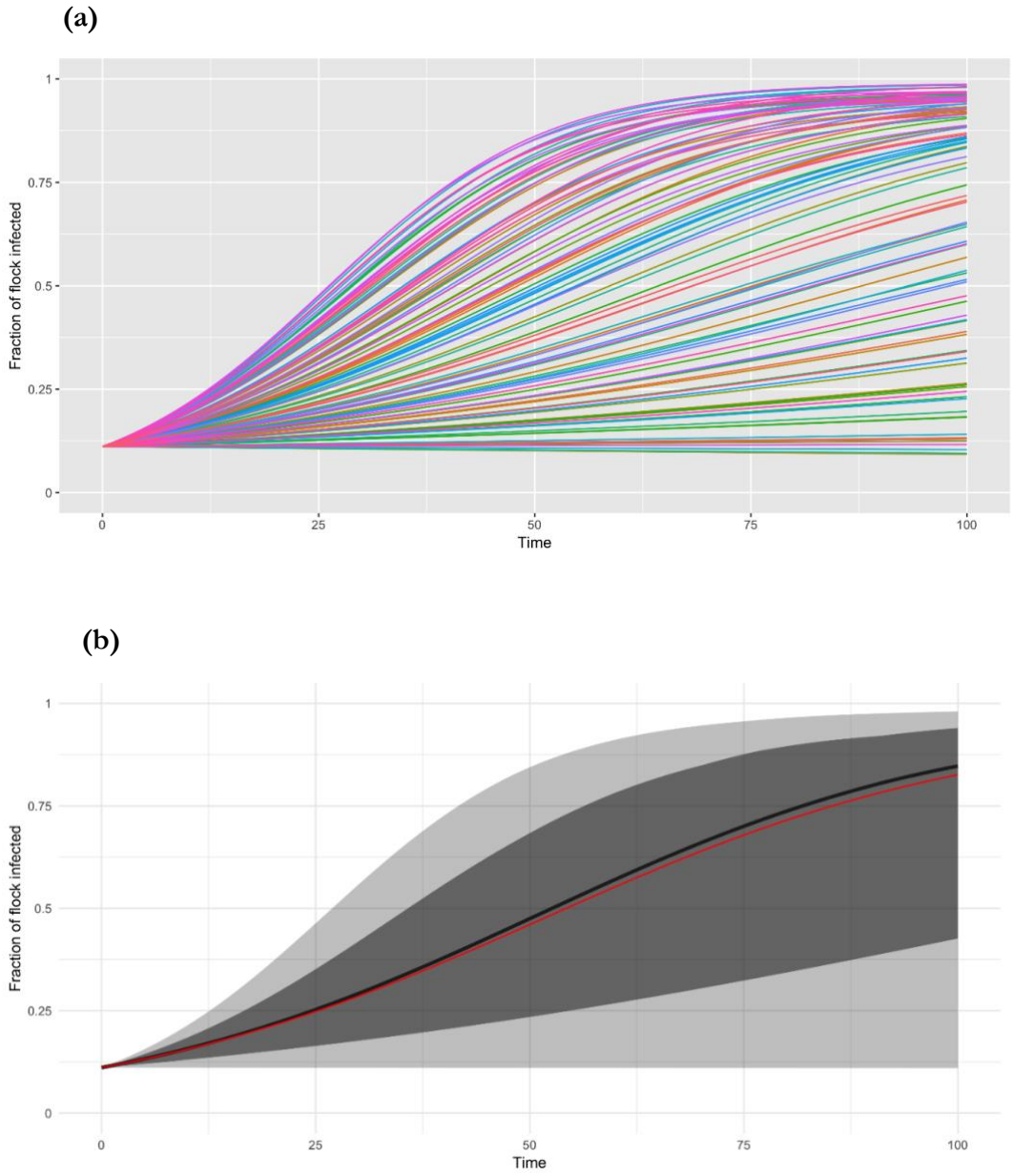
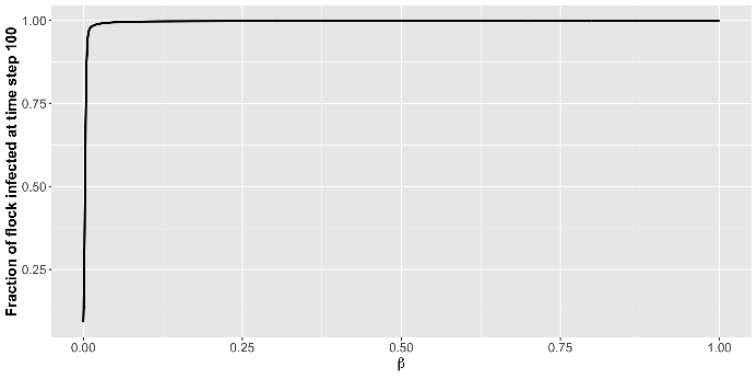


Fig. 2.7. Latin Hypercube Sampling Sensitivity Analysis of the transmission rate (β), recovery rate(γ), disease-induced mortality rate (*m*) and the restocking rate (ξ) in a deterministic version of a within-farm SITD model of sheep scab. The PDF range was 100% above and below the baseline parameter values for β, γ and *m* and from 0 to 1 for ξ. At time step one, 1/9 sheep is infected. The PDF distribution was uniform for all parameters. (a) The fraction of flock infected over 100 time steps is are given for 100 parameter combinations (N=100). (b) The results are summarised, showing the median result (black line), interquartile ranges (dark grey shading) and 97.5th and 2.5th percentiles (light grey shading). The red line in (b) indicates the result from the R deterministic run of the model under the baseline parameters specified in section 2.3.3.

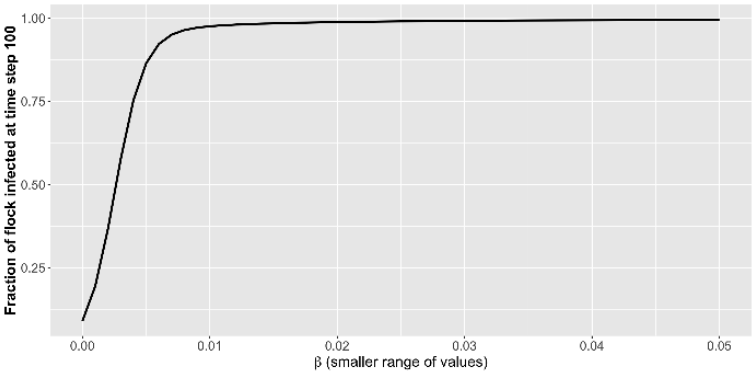
2.4.2.2 Relationship between parameters and model output in one-at-a-time sensitivity analyses

The relationship between each parameter and the model output is non-linear and monotonic (Fig. 2.8), which means that a PRCC can be used on the LHS results to measure the importance of each parameter to the model output (Fig. 2.9).

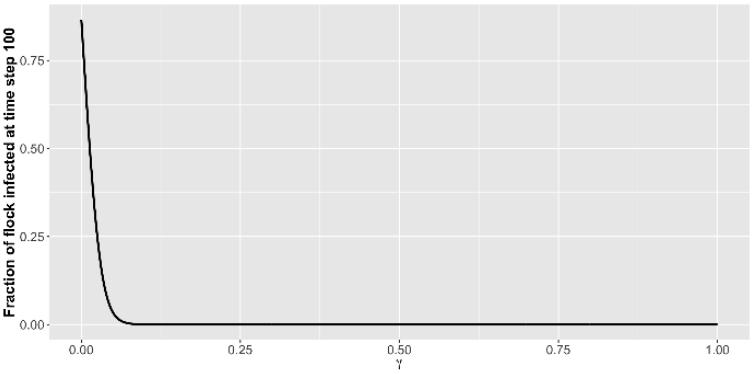
a (i)


Fraction of flock infected at time step 100
1.00
0.75
0.50
0.25
0.00
0.25
0.50
0.75
1.00
β

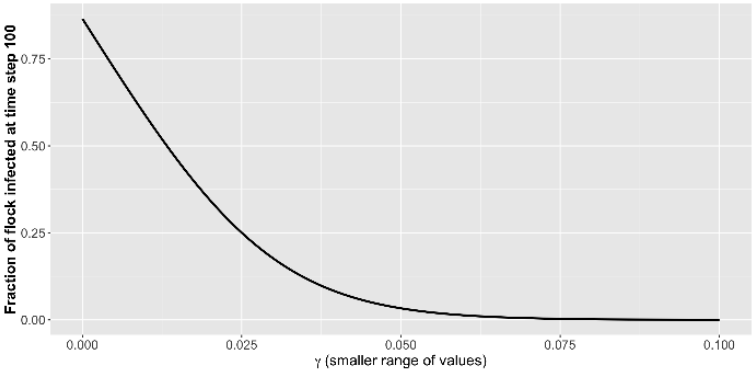
(ii)


Fraction of flock infected at time step 100
1.00
0.75
0.50
0.25
0.00
0.01
0.02
0.03
0.04
0.05
β (smaller range of values)

b (i)


Fraction of flock infected at time step 100
0.75
0.50
0.25
0.00
0.25
0.50
0.75
1.00
γ

(ii)


Fraction of flock infected at time step 100
0.75
0.50
0.25
0.00
0.000
0.025
0.050
0.075
0.100
γ (smaller range of values)

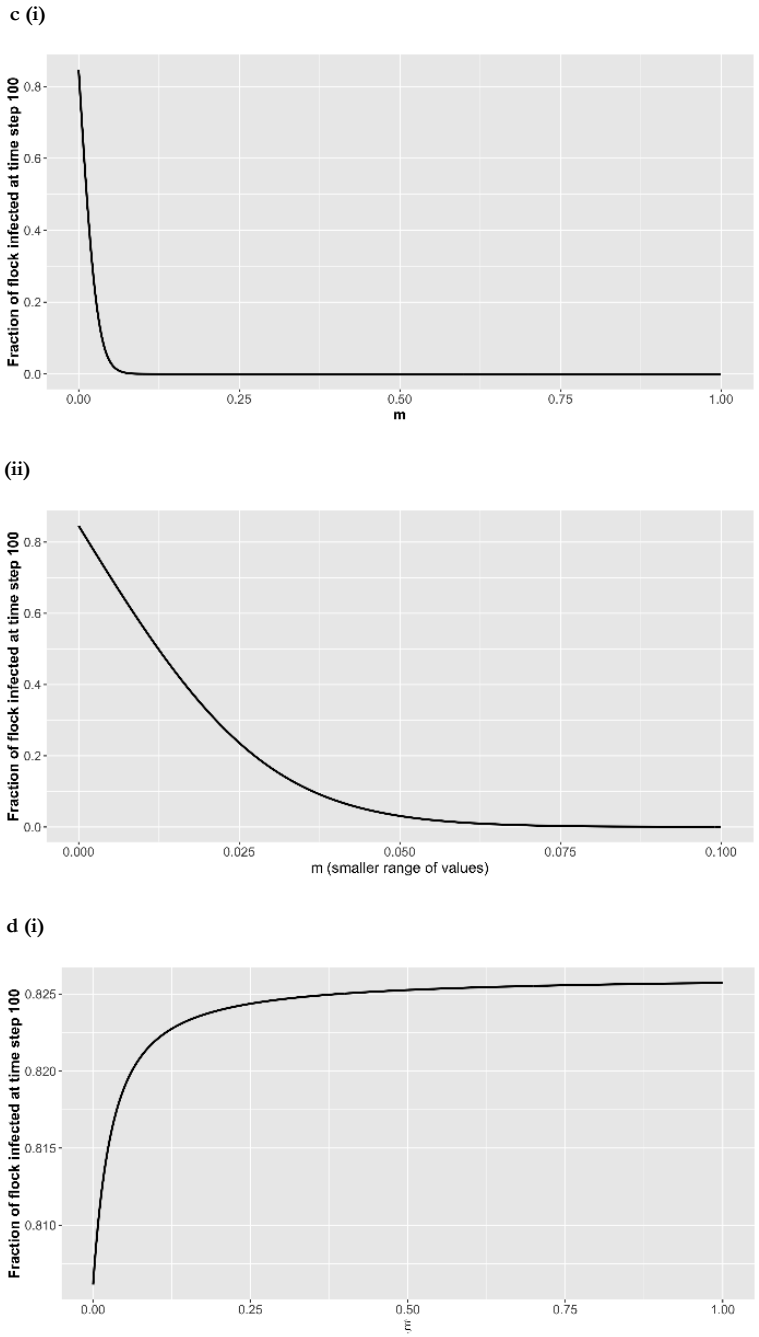


Fig. 2.8. Relationship between four parameters and the model output when all other parameters are kept at a baseline level and the parameter of interest is varied from 0 to 1 by 0.001. The parameters investigated were (a) transmission rate, β, (b) recovery rate, γ, (c) infectious mortality rate, *m* and (d) restocking rate, ξ. Figures which show the full range of parameter values used are labelled (i) and those which show a smaller range to give more insight into the relationship are labelled (ii). The model output given is the fraction of the flock infected at time step 100 when 1 sheep was infected with sheep scab at time step 0 and 8 sheep were susceptible. These results are from the deterministic version of the within-farm SITD model of sheep scab.

2.4.2.3 Partial rank correlation coefficient

A partial rank correlation coefficient was carried out for each parameter of interest. At time step 100, there is a strong, significant, positive correlation between β and the model output (PRCC = 0.93 (2dp), $p = 1.25 \times 10^{-43}$), a weak, non-significant, positive correlation between ξ and the model output (PRCC = 0.10 (2dp), $p = 4.25 \times 10^{-1}$), a weak, significant, negative correlation between γ and the model output (PRCC = -0.20 (2dp), $p = 4.12 \times 10^{-2}$) and between m and the model output (PRCC = -0.27 (2dp), $p = 7.5 \times 10^{-3}$).

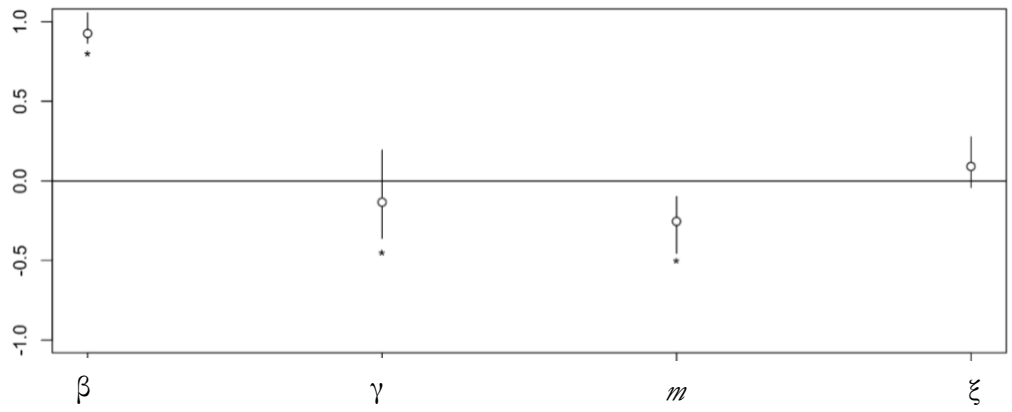


Fig. 2.9. Partial rank correlation coefficient on Latin Hypercube sampling for parameters in the deterministic version of the within-farm SITD model for sheep scab. The parameters investigated included transmission rate (β), recovery rate (γ), disease-induced mortality rate (m) and restocking rate (ξ). The results were from the LHS with PDF range 100% above and below the baseline values for β, γ and *m* and from 0 to 1 for ξ. The output observed was the number of sheep infected at time step 100. A star indicates that the p value for the PRCC was less than 0.05 for the test statistic of the significance that the partial rank correlation coefficient is greater than or less than zero. The error bars indicate the confidence level of the bootstrap confidence intervals when there are 1000 replicates and the confidence level of the bootstrap confidence intervals is 0.95.

2.5 DISCUSSION

The model described in this chapter can be used as a stand-alone model to investigate the within-farm transmission dynamics of sheep scab, but also forms a baseline component for a larger between-farm transmission model that will be described in Chapter 3.

2.5.1 Initial results from the model and from the model testing

Overall, the results from both the stochastic and deterministic versions of the model follow a similar trend to the Berriatua et al. (1999) experimental data, with the fraction of the flock infected increasing over time and with the majority being infected after 100 time steps (days) (Fig. 2.3, Fig. 2.4). As the transmission rate was estimated using this experimental data, this is to be expected. If other data become available that would allow for further comparison, this may lead to further improvements in the accuracy of the model.

Although the general trend was the same between the experimental and the model data, the median result for the model data was less than the median result for the experimental data at almost all time steps (Fig. 2.3, Fig 2.4). In addition, the model output and the experimental data were not found to be from the same distribution when using a Pearson's Chi-squared test for count data. The final fraction infected on day 100 was the highest for the experimental result (median =1), followed by the R deterministic model (0.81) and was the lowest for the stochastic model (median = 0.78). The deterministic result was within the percentile range (2.5-97.5) for the experimental results, however, for some iterations, the median stochastic result was below the 2.5th percentile of the experimental data.

This trend of fewer sheep becoming infected in the model compared to the experimental results could be because of the influence of the range of parameters in the model which were estimated using other data. Another explanation may be that the difference between one of the experimental replicates (40% infected after 100 days) and the other four replicates (100% infected after 100 days) is reflected in the transmission rate of the model, but is not reflected in the median, the interquartile range and 2.5-97.5 percentiles of the experimental data (Fig. 2.4). Since the experimental data had only five replicates, this experimental result could not be considered as an outlier. Another explanation for the underestimation in the model

output compared to data could be related to the fact that sheep are assumed to have the same infectiousness across the whole course of their infection, whereas this is likely to vary along with the number of mites they harbour. The model described. in this chapter is expanded and reparameterised in Chapter 4 in order to investigate why underestimation may have occurred.

Although the median stochastic result was broadly consistent with the deterministic result, the variability in the output may more accurately reflect reality than the deterministic model, (Fig. 2.3, Fig. 2.4). As seen in the experimental results, outbreaks of sheep scab do not always have the same outcome. The wide confidence interval for the stochastic results shows that the model allows for the variation seen in reality, including extinction of the disease. This is thought to be particularly important when the population size is small (Keeling & Rohani, 2008), as seen in the simulations here. In addition, this stochastic model gives the number of sheep as integers, rather than decimals. However, running the model stochastically is much more computationally expensive than running it deterministically and it is more difficult to fit to data. When possible, the model should be run stochastically, but if this is not possible, then the deterministic result will still give a good indication of the disease dynamics and could be used to fit the model to data. In addition, deterministic models are usually thought to be simpler to understand and to develop than stochastic models (Diekmann et al., 2013).

The results from all three iterations of the LHS match the positive correlation between time and the fraction of flock infected seen in the model results (Fig. 2.5, Fig. 2.6, Fig. 2.7). However, as the PDF ranges increase for each iteration of the LHS, so do the confidence intervals, which is to be expected. As the PDF distribution was uniform, it is expected that the variability in the output seen here is more extreme than if a different distribution had been used. In addition, as the correlations between the parameters were not included, this may have also increased the variability in the results.

The OAT analyses (Fig. 2.8) and the PRCC (Fig. 2.9) both demonstrated that β has the strongest positive relationship with the model output. The PRCC indicated that this relationship is strong and significant and that β is the most sensitive parameter. Although there was a significant negative relationship between γ (recovery rate) and the model output and between m (the disease-induced mortality rate) and the model

output, these relationships were much less strong. Interventions that help to reduce β (transmission rate) may therefore be most important when trying to control sheep scab. As the model is density dependent, then reducing stocking density is likely to help reduce the transmission rate. Quarantining infected sheep will also help to reduce R_0 and henceforth β. Restocking does not have a significant impact on model results so it is unlikely to be something that is useful to target in future interventions. However, a different result may have been seen over a longer time period.

The protection rate and protection loss rate were not included in the UA and SA. This is mainly because they are different to other parameters as they change at different points during a simulation depending on when treatment is used. Future work could perform UA and SA solely on these two parameters to investigate when it might be most effective to use treatment and what proportion of the flock should be treated.

2.5.2 Limitations of the model and model testing

2.5.2.1 Limitations of the choice of modelling software

In this chapter, the model was built in both R and STEM and the results between the models were very similar, despite the fact that the version developed in R was deterministic and the version in developed STEM was stochastic (note that it is possible to create deterministic and stochastic versions of the model in both programs). R was used as it gave full control over the model, while STEM was used to make use of the in-built plugins that reduce programming time. The similarity between the results is encouraging and suggests, at least for the model developed in this chapter, that a model user could decide to use either software depending on their user preferences, without concern that one version is more accurate than the other.

2.5.2.2 Limitations of the model development choices

The choice to use a micro-parasitic modelling method to model a biological macro-parasite may have impacted the accuracy of the results. In particular, with this, the assumption that the infectiousness of an index case is the same, regardless of the number of mites they harbour. It has been suggested that as long as one pregnant

female mite is on a host, it can spread to another host and cause infestation (van den Broek & Huntley, 2003b). However, Bates (2012) claims that sheep with subclinical scab do not transmit mites to other hosts or to the environment and that transmission only occurs when the mite populations have reached a certain level. Without clinical evidence, no conclusions can be made about at which stage of the condition *P. ovis* mites can be transmitted. However, a study which developed a Leslie-matrix model for the life-cycle and population growth of *P. ovis* on a single sheep (Wall et al., 1999) could perhaps be incorporated into a within-farm transmission model of sheep scab in the future, assuming that the risk of transmission from an index case increases with the *P.ovis* population size on the host. A simple way to incorporate this could be to include multiple compartments for infectious individuals in the model, with the rate of movement between the compartments determined by the *P.ovis* population numbers seen over time, with higher population numbers giving an increased risk of transmission. Not including the impact of the life-cycle and population size of *P.ovis* on the host in the model described in this chapter may have led to more individuals becoming infected more quickly in the model than as seen in reality. However, the results do not seem to reflect this, with slightly fewer individuals infected in the model than as seen in reality (Fig. 2.3., Fig. 2.4). However, including the on-host life-cycle and population size of *P.ovis* still might help to improve accuracy in future models. In Chapter 4, an extra compartment is added for sheep which have passed the peak of infection and therefore harbour less mites.

In the study by Berriatua (1999), transmission between an infectious and a susceptible individual was assumed to have occurred when either increased rubbing in the susceptible individual first occurred, or when the presence of early scab lesions in the susceptible individual were first detected. In reality, the transmission of the mite will have occurred before these signs were detected (Bates, 1997a). As the transmission parameter was estimated using data from Berriatua (1999), this may mean that the model might have underestimated the time it takes for an infectious individual to transmit scab to a susceptible individual. However, without using a diagnostic test such as the Enzyme-linked immunosorbent assay (ELISA) for sheep scab (Nunn et al., 2011) on a daily basis, it is not possible to calculate exactly when transmission has occurred in such an experiment and, even then, the sensitivity and specificity of the current ELISA are only at 98.2% and 96.5% respectively (Busin et

al., 2018b). Future experiments looking at within-farm transmission of sheep scab should attempt to use ELISAs to calculate a more accurate transmission time.

In this basic version of the model, sheep were moved from the infectious to the susceptible compartment if they recovered. However, there is some evidence that secondary infestations are less severe. In a study by Bates (2000), previously infected sheep (n=3) were reintroduced to scab a year following their recovery and became infected, but the lesion and the mite burden remained sub-clinical for at least fifty days, suggesting that some host resistance to the mites had been acquired. Clinical sheep scab was observed later in the study once mite colonies had established, but the mite numbers remained low. Spence (1949) also found that in re-infestations of scab, mite populations increased more slowly. It is not certain whether this observed host resistance is mainly due to an immunological response or whether there are other factors. Van Den Broek et al. (2000) found that lesions were smaller and there were higher levels of serum IgE in re-infestations. However, there are also suggestions that the skin of sheep that have recovered from sheep scab may be less suitable for mites to feed on during re-infestation (ADAS, 2008). As the model described here is not an agent-based model and assumes that individual behaviour is homogenous, it would not be possible to track individual sheep and to use different parameter values for sheep with a second infestation. However, there could be potential for future development of the current model using a different susceptible compartment for sheep which have already been infected.

Indirect and direct transmission were not distinguished in this model. In future, if data on this were available, it might be interesting to include these as separate parameters. This might help identify control methods which focus on the different aspects of transmission and also might lead to more accurate transmission results in the model.

The model presented in this chapter assumes that the time-scale for the spread of scab is quick enough that births and deaths do not impact the dynamics. However, in future versions of the model, if the simulated time is to last for more than a few months, then it would be important to include natural births and deaths. This is because in sheep flocks, lamb births and their later slaughter, lead to large variations in population size over a one year period and changes in population size are known to impact disease dynamics (Keeling & Rohani, 2008). In addition, it might be

important to investigate the variances between lambs and ewes that might lead to different estimates of the disease parameters or different restrictions on treatment choices. For example, lambs born to ewes with severe sheep scab were shown to have high mortality rates (Sargison et al., 2006), although quantitative data for calculation of the mortality rate was not provided in the study. In addition, lambs which weigh between 5 and 20kg cannot be plunge- dipped safely (Sargison et al., 2006) and Sargison et al. (2006) report that injection of systemic endectocide in lambs is impractical. Therefore, it might be important to include age into the model when planning treatment strategies and generally, so that the variation between age groups of sheep is included in the disease parameters.

2.5.2.3 Limitations of the parameter estimation

As already discussed, a limitation of the experimental data that was used to estimate the transmission rate (Berriatua et al., 1999) is that there were only five replicates; more replicates would have increased the reliability of the estimation. Here the final size across all five experiments was used to calculate the transmission rate, however, if the final size from each experiment (Table 2.3) had been used to create a distribution for the transmission rate, then this might increase model accuracy, since there was some variation in the final size between experiments.

However, the final size for each experiment may have been underestimated. If the experiments had continued for longer than 14 weeks then the final size may have been greater. In the study, scab was only diagnosed by clinical observation and not with potassium hydroxide (KOH), centrifugation and microscopy, which, although are thought to be superior diagnostic tools to clinical observation alone, have been found to have success rates as low as 18% (Bates 2009). Therefore, it is highly likely that the success rate of the clinical observation used to diagnose scab in the study may have been even lower. This may have been particularly important where there were issues with the experiments in the study, for example, Trials 1A and 1B were initially one trial, but then the index case had to be removed due to welfare issues and the group was divided in two, one with a new index case and the other with a newly infected case who had become infected in the first part of the trial. However, as sheep scab can be hard to detect and the authors do not note how they diagnosed the "susceptible" sheep once the two groups had been split, it is likely that some of the susceptible individuals may have become clinically infested in the first half of the

trial. In addition, the index case in Group 2C was treated and cured due to welfare issues. Taking all this together, it seems likely that the final size used to estimate the transmission rate is an underestimate. However, without more data on the within-farm dynamics of sheep scab, it is difficult to improve this estimate.

The limitations of the diagnostics used in the study by Berriatua (1999), is also likely to have reduced the accuracy of the timing of the transmission events recorded. Transmission between an infectious and a susceptible individual was assumed to have occurred when either increased rubbing in the susceptible individual first occurred, or when the presence of early scab lesions in the susceptible individual were first detected. In reality, the transmission of the mite will have occurred before these signs were detected (Bates, 1997a). As the transmission parameter was estimated using data from Berriatua (1999), this may mean that the model might have underestimated the time it takes for an infectious individual to transmit scab to a susceptible individual. However, without using a diagnostic test such as the Enzyme-linked immunosorbent assay (ELISA) for sheep scab (Nunn et al., 2011) on a daily basis, it is not possible to calculate exactly when transmission has occurred in such an experiment and, even then, the sensitivity and specificity of the current ELISA are only at 98.2% and 96.5% respectively (Busin et al., 2018b). Future experiments looking at within-farm transmission of sheep scab should attempt to use ELISAs to calculate a more accurate time to transmission.

The results from the Berriatua study might not be transmissible to 'real – world' transmission in a sheep flock where the sheep breeds are different from those used in the study, as It has been suggested that differences between sheep breeds such as fleece microclimate or skin physiology may impact the likelihood of a sheep contracting scab (Smith et al., 2001). The sheep used in these experiments were cross-breeds from the Veterinary Laboratories Agency's flock. Therefore, the results from this study are not necessarily applicable to all sheep breeds. In addition, the stocking density of sheep in the Berriatua study is not reflective of the stocking density of all sheep flocks in Great Britain, which can vary widely from ~1 per $1000m^2$ (6 sheep per acre in average grassland) to $500/1000m^2$ (smallest value for lambs from up to 12 weeks of age on straw-bedded floor) (National Sheep Association, 2020a). The stocking density for the experiments in the Berriatua et al. (1999) study ranged from 289 to 420 sheep per $1000m^2$ (Table 2.3). Therefore, the

results from Berriatua are most representative of farms which have a high stocking density on average.

The estimation of the restocking rate was not based on any specific data from the literature; however, it was shown to not be sensitive to the model at time step 100 in the sensitivity analysis (Fig. 2.9). Even so, this is not necessarily reflective of its importance at other time steps. Continuously adding susceptibles to the model affects disease dynamics (Keeling & Rohani, 2008), often allowing the new epidemics to occur when the disease would otherwise have died out and so this may be an impact of including a restocking rate, particularly as the model is density-dependent. As suggested by Anderson (1982), maintaining a constant flock size could be counter-productive, since a reduction in host density reduces the basic reproductive rate of a parasite. It also may not be realistic to assume that farmers will instantly restock when disease mortalities occur. A Markov chain simulation model of Maedi-Visna disease of sheep (Stott et al., 2009) maintained a constant flock size by restocking ewes lost to the disease on an annual basis. Better estimates of realistic restocking rates for ewes might be useful for future models. However, as the current model assumes a constant ewe population size, a value of 1 is considered to be appropriate here.

2.5.2.4 Limitations of the choice of sensitivity analysis techniques

The combination of LHS and PRCC was found to be one of the most widely applicable UA and SA techniques in a review of five global sensitivity analysis techniques for infectious disease modelling (Wu et al., 2013). A disadvantage of this combined technique is the rank, rank-residual and related PRCC at one simulation time step cannot be directly compared with those from another time step, yet temporal effects may be important in epidemiological modelling. For example, if sensitivity is only calculated at a time step that occurs after the epidemic peak, then parameters that were important in the growth of the epidemic curve may no longer seem important (Wu et al., 2013). This is a limitation of the sensitivity analysis done in this chapter, as the PRCC was only done at time step 100. In future, the Morris method (Morris, 1991) or the sensitivity heat map method (Rand, 2009) could be used as these allow for comparison of parameter sensitivity across simulation time steps.

The literature suggests that when selecting the number of replicates for the LHS (N), this should be at least K + 1 (K being the number of parameters under investigation) (Marino et al., 2008). Another suggests that N must be greater than 4/3K (Mckay et al., 1979). McKay (1988) later suggests that N = 2K, while Manache & Melching (2007) suggest that is should be at least 3K and at an appropriate significance level for the PRCC. In the LHS carried out in this chapter, N= 100 and seeing as K is four, our value for N supersedes even with the most conservative approach of N=3K. Therefore, it is likely that an accurate number of probability intervals was used for the LHS.

2.6 CONCLUSION

Overall, the model presented in this chapter appears to give a good representation of the dynamics of sheep scab seen within flocks in experimental studies. It can therefore be used as a stand-alone model to investigate the within-farm dynamics of sheep scab, or as part of an expanded models that include between-farm transmission, such as the model described in Chapter 3 which simulates sheep scab transmission across Great Britain. However, the model, as parameterised, does underestimate the rate at which sheep become infected over a period of 100 days when compared to the experimental data. The reasons for this are explored further in Chapter 4.

Chapter 3

MODELLING THE SPATIAL DYNAMICS OF SHEEP SCAB ACROSS GREAT BRITAIN

SUMMARY

Following 21 years in which scab was eradicated in Great Britain, it was inadvertently reintroduced in 1973 and despite the implementation of a range of control methods, has remained endemic thereafter. The prevalence varies across different regions, being the highest in Wales (15.8%), Scotland (14%) and Northern England (11%). Following the reintroduction, it was thought that transmission occurred through the sale of infested sheep at markets and contact with neighbour's sheep. This chapter expands the within-farm sheep scab transmission model described in Chapter 2 to incorporate between-farm transmission via contact with neighbours, using an SIR metapopulation model approach. The model is tested first by running a simulation using the same farms in north west England that were initially infected in the 1973 reintroduction and the model results are compared to the observed outbreak data from the 20 years after 1973. The model shows that disease spreads for the first few years after introduction, but then self-limits for the remaining 13 years. This pattern of self-limitation is repeated when the model is run with outbreaks at the same number of initially infected farms but in a different location (south west England). The incidence of scab is much higher in the model results than in the reported data and the reasons for this are discussed and further investigated in Chapter 5. The spatial model results are in contrast with the pattern seen in the reported outbreak data from those years, where sheep scab spread rapidly across the whole of Great Britain. It is concluded that the difference is likely to be due to the fact that the model incorporates only between-farm transmission; the inference is that long-distance movements are critically important in the national transmission of scab. Examination of the model network shows that that there are clusters of farms with high connectivity and with a high R_0. This result suggests that future control should focus on the management of infested sheep at markets and any long-distance movements from these farm clusters.

3.1 INTRODUCTION

After 21 years during which scab was presumed to be eradicated in Great Britain, on the 1st January 1973, sheep scab was confirmed as present in a flock in Lancashire. Subsequent investigations found that there were other outbreaks in the area, with 11 flocks confirmed to have sheep scab from 1st to 25th of January 1973 in Lancashire, 15 in the West Riding or Yorkshire and one in Cheshire. All these cases were traced back to a flock where sheep scab was thought to have been introduced from imported sheep from Ireland. A Movement Restrictions Area order was put into place for a year where a summer and autumn acaricide dip were enforced for all sheep (Loxam, 1974). However, this did not prevent transmission and scab subsequently spread. This was followed by a series of compulsory regional and then national acaricide treatment programmes that were imposed from 1973-1992, but sheep scab continued be prevalent throughout Great Britain (French et al., 1999).

Today the prevalence of sheep scab in Great Britain is approximately 9% (Bisdorff et al., 2006; Rose, 2011), with a particularly high prevalence found in Wales (15.8%) (Chivers et al., 2018), Scotland (14%) and Northern England (11%) (Bisdorff et al., 2006). Since 1992, the choice of which prophylactic or therapeutic treatments to use for scab is left to individual farmers (from within an approved list of potential treatments), although prophylaxis is optional while treatment of confirmed outbreaks is compulsory under the 'Sheep Scab Order' (MAFF, 1997) and cases in Scotland must be reported (Scottish Government , 2010).

Sheep scab can be introduced into a farm via buying in sheep, strays (Sargison et al., 2006), having neighbours with scab and through the use of common grazing (Rose & Wall, 2012). In particular, farms using common grazing, farms that have direct contact with neighbour's sheep and farms that have neighbours with scab have been found to be most at risk (Rose & Wall, 2012). Transmission of scab between neighbouring farms is thought to occur via physical contact at farm boundaries, but also through wool tags on fencing (Henderson, 1990), sharing handling equipment and transportation vehicles (Sargison et al., 2006).

At the time of the reintroduction of sheep scab in Great Britain in 1973, it was considered that that there were only two major factors that had contributed to sheep scab spread across Great Britain: the buying in and introduction of infected sheep

into a naïve flock and the contact between infested naïve flocks during grazing. At that time, it was considered that there was no evidence that scab might be transmitted during contact in markets (Loxam, 1974). Subsequently however, this method of sheep scab transmission has been demonstrated (Bates, 2007) although its relative importance is unknown.

This current chapter describes work which aimed to build a spatial model of the transmission of sheep scab between farms. Such a model could be of considerable value, helping to identify targets for improved control. This chapter therefore builds upon the work described in Chapter 2, where the classic SIR model (developed by Ross (1915) and expanded on by Kermack & McKendrick (1927)) was adapted to simulate within-farm transmission of scab, to include a between-farm characteristic of the model. The traditional SIR model does not incorporate the spatial aspects of disease transmission and assumes homogenous mixing within a population (in Chapter 2 this is the sheep population in one farm). To model between-farm transmission of sheep scab, therefore, the traditional SIR model approach must be expanded.

There have been various methods developed to spatially extend SIR models. Plant epidemiologists have adapted the SIR differential equations into integro-differential equations, focusing on independent pathogen movement (Madden et al., 2007). Others have converted the SIR equations in reaction-diffusion equations (van den Bosch et al., 1988). Another method has been to assume each individual is a node in a network and that transmission occurs between individuals when their two nodes are connected by an edge (Kleczkowski et al., 2019).

Metapopulation models are similar to network models, however instead of explicitly modelling the transmission between individuals, the transmission of disease between and within groups is modelled. Geographical space is compartmentalised, with the assumption of homogenous mixing within each compartment. An additional force of infection is applied to each compartment from other compartments, which is sometimes dependent on the distance between them (Harwood et al., 2009; Meentemeyer et al., 2011). The model presented in this chapter is a metapopulation model, with transmission occurring within and between sheep farms.

3.2 AIMS

This chapter aims to describe the expansion of the within-farm transmission model in Chapter 2 to include between-farm transmission across all sheep farms in Great Britain via neighbour-neighbour contact, by developing a metapopulation model. The chapter then aims to investigate and test the model, primarily by running a simulation based on outbreak data from the 1973 reintroduction of sheep scab into Great Britain and then comparing the model outputs with the known spatial outbreak pattern for the 20 years after 1973.

3.3 METHODS

3.3.1 Overall Model structure

Here the stochastic model described in Chapter 2 is extended to also include between-farm transmission including all sheep farms across Great Britain. The software used for this is the Spatial Temporal Epidemiological Modeler (STEM) (Ford et al., 2006; Douglas et al., 2019). This was used to build a metapopulation model whereby transmission of scab between neighbouring farms (subpopulations) is modelled by movements of equal numbers of sheep between neighbouring farms on a daily basis. The proportions that move are different between farms that use common grazing and those which don't. For the purposes of this chapter, it was assumed that transmission of scab was only possible via contact between neighbouring farms, however long-distance movements are included in the model presented in Chapter 5. The parameters used for within-farm transmission in the model are the same as given in Chapter 2.

3.3.2 Model description

The deterministic equations that describe the model in Chapter 2 are expanded here in order to include the movement between neighbouring populations (farms). The following equations describe the rate of change in population sizes in a farm *i* according to both dynamics within *i* and movements of sheep between i and all neighbouring farms *j*:

$$\frac{dS_i}{dt} = \gamma I_i + \xi D_i + \theta T_i - \beta_i S_i I_i - \Psi S_i + \sum_j (S_{ji} - S_{ij}) \quad 3.1$$

$$\frac{dI_i}{dt} = \beta_i S_i I_i - \Psi S_i - \gamma I_i - m I_i - \Psi I_i + \sum_j (I_{ji} - I_{ij}) \quad 3.2$$

$$\frac{dD_i}{dt} = m I_i - \xi D_i + \sum_j (D_{ji} - D_{ij}) \quad 3.3$$

$$\frac{dT_i}{dt} = \Psi (I_i + S_i) - \theta T_i + \sum_j (T_{ji} - T_{ij}) \quad 3.4$$

where S_{ij} is the number of susceptible sheep that move from farm *i* to farm *j* on a daily basis and S_{ji} is the number of susceptible sheep that move from farm *j* to farm *i*

on a daily basis. The equivalent parameters for the other compartments have the same meaning but for the number of sheep in their respective compartment.

The movement of equal numbers of sheep between neighbouring farms to simulate mixing is a stochastic process whereby the number of sheep that move between the farms is selected from a binomial distribution based on the mixing rate between farm *i* and farm *j* (σ_{ij}) and the number of individuals on farm *i* (N_i):

$$N_{ij} = Binomial(\sigma_{ij}, N_i) \quad 3.5$$

The value of N_{ij} is then allocated equally between the compartments in the disease model:

$$S_{ij} = round(N_{ij} * \frac{S_i}{N_i}) \quad 3.6$$

$$I_{ij} = round(N_{ij} * \frac{I_i}{N_i}) \quad 3.7$$

$$D_{ij} = round(N_{ij} * \frac{D_i}{N_i}) \quad 3.8$$

$$T_{ij} = round(N_{ij} * \frac{T_i}{N_i}) \quad 3.9$$

while ensuring $N_{ij} = S_{ij} + I_{ij} + D_{ij} + T_{ij}$.

The mixing rate is equal between pairs of subpopulations $\sigma_{ij} = \sigma_{ji}$ and so subpopulation sizes are maintained (Fig. 3.1). As with the other model parameters, the mixing rate is a daily rate.

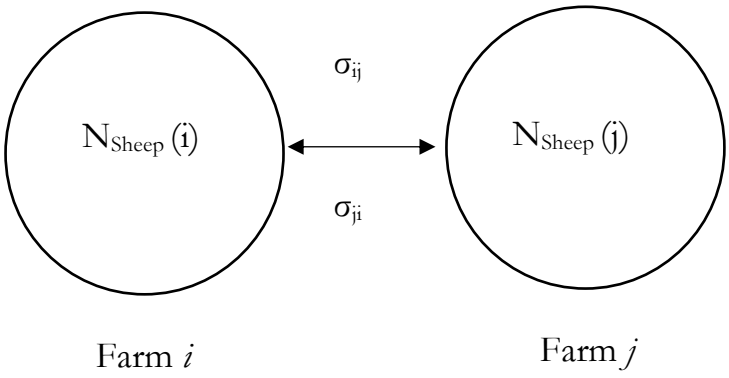


Fig. 3.1 Schematic showing migration of sheep between two subpopulations in the metapopulation model. The circles represent farms, which are subpopulations. There is a bi-directional edge between the two farms indicated by the arrows. The populations of sheep on each farm (i and j), move between farms at a daily migration rate (σ_{ij} or σ_{ji}). This figure is based on a figure from the STEM wiki (Edlund et al., 2013).

3.3.3 Implementation of the model in STEM

3.3.3.1 Networks in STEM

Metapopulation models in STEM are built as networks of populations, with nodes containing populations and edges the ability for movement to occur between the populations. The network can be formulated as a square lattice, built from a pajek file or from an ESRI Shapefile (Kaufman et al., 2017). In a pajek file, migration edges are specified between nodes and allow individuals in a population to move between connected nodes at a certain rate (migration rate, σ, the proportion of population to move per time step) and in a certain direction (Fig. 3.1). It is possible to have multiple populations at one node, for example, humans and birds, and so the population that is to migrate must be specified. When two migration edges are used between two nodes, where each edge has the same rate but an opposite direction (bi-directional migration edges), this is used to simulate mixing of proportions of populations (equivalent to the mixing rate, σ) and the possibility of transmission between them (Fig. 3.1). Migration edges can be continuous (applied at each time step) or the date at which they are to be applied can be specified (Edlund et al., 2013; Douglas et al., 2018b).

In the network described here, continuous bi-directional migration edges with the same migration rate ($\sigma_{ij} = \sigma_{ji}$) are formed between farms which are considered to be neighbours (Fig. 3.1). As the bidirectional migration edge approach is used to simulate contact between sheep from different farms, and migration is not used in the model versions described here, this approach will be referred to as "mixing" for the remainder of the chapter. The "mixing rate" will refer to the rate that is used in both directions on the migration edges. The network of subpopulations in this chapter was based on sheep farm location data (eastings and northings) provided by APHA (see section 3.3.3.3) and so was produced using a pajek file in STEM (Douglas et al., 2018b).

3.3.3.2 Calculating the mixing rate (σ)

The mixing rate (σ) is specified as a proportion, where 1 is the whole population. Three different mixing rates are used in the network described here (Table 3.1).

Common grazing, a practice where sheep from different farms graze together on common land, has been found to increase the risk of a flock having scab by almost tenfold (Rose & Wall, 2012). In a study looking at the behaviour of sheep on common grazing it was found that, on average, 51.36% (range 41.10-70.73%) of the core range of a flock (where sheep were found 50% of the time and where most activity occurs) was shared with at least one other flock (Rose & Wall, 2012). This result was used as an estimate for a proportional daily mixing rate of 0.5136 between two farms which both use common grazing in the model. The core range rather than the home range was used to calculate the mixing rate because this is the area within which the majority of the flock would be on a day-to-day basis.

In interviews with sixteen farmers who had experienced repeated outbreaks of sheep scab, it was found that using common grazing increased the likelihood of getting scab by a factor of 10 compared to farms which do not (Rose & Wall, 2012). Therefore, in the models described here, the daily mixing rate (σ) between neighbours where only one or neither of them uses common grazing was estimated at ten times less than when both farms used common grazing (0.05136).

Scottish Islands are assumed to be separate units as neighbour-neighbour transmission of scab is not possible across water boundaries. Within an island, however, mixing of sheep between farms occurs freely (personal communication Professor Neil Sargison). Therefore, it was assumed that sheep from all farms on any one Scottish Island mix with sheep from all other farms and each Scottish island is treated as one farm unit.

Table 3.1 The mixing rate between farms according to their specific characteristics as described in section 3.3.3.2

	Farms using common grazing	**Farms not using common grazing**	**Farms on Scottish islands**
Farms using common grazing	0.5136	0.05136	n/a
Farms not using common grazing	0.05136	0.05136	n/a
Farms on Scottish islands	n/a	n/a	1

3.3.3.3 Sheep holding data source

The data on Great Britain sheep holding locations in 2014 were provided by the Animal and Plant Health Agency (APHA) and will be known as the "APHA data" in this chapter. The name of each column and type of data provided is given in Table 3.2. The population at each holding is given by the column "NumberofSh" which is assumed to be the number of ewes per holding, although the data providers were unsure of whether this also included the number of lambs and rams. No information was provided about the original data source, although it is assumed this was the Sheep and Goat Inventory as the data matches that description (Animal and Plant Health Agency – APHA, 2018a). This data is collected in December (England) and January (Scotland and Wales) and offers a snapshot of the number of sheep at the date of the survey. Lambs are usually not present in flocks in December and January and therefore it is assumed that the "NumberofSheep" refers to the number of ewes only (APHA, 2018a). The locations of the sheep farms provided by APHA are assumed to be the central point of that holding and are identified via their County Parish Holding (CPH) number. A CPH can cover land and buildings up to 16km away from the main livestock handling area (Department for Environment, Food and Rural Affairs- DEFRA, 2018a).

Table 3.2 Column names and descriptions of data provided by the APHA on the locations and populations of sheep holdings in Great Britain.

Name of column	Description of data
Numberofsh	Integer. This was assumed to be the number of ewes in a flock.
CPH	The is the County Parish Holding Number, a unique number used to identify holdings. The format is 00/000/0000, with the first two digits referring to the county, the following three to the parish and the final four to the holding (British Government, 2016).
GISPostcode	The Postcode relating to the postal address of the CPH owner.
Best Easting	Easting of the primary grid reference for the CPH. On an online form for a temporary CPH number this specifies that it should be the "animal gathering point or access point for the temporary holding" (DEFRA & APHA, 2017).
BestNorthing	Northing of the primary grid reference for the CPH number.
Year	This was 2014 for all CPH holding data provided.

3.3.3.4 Sheep holding data processing

The total number of farms in the original dataset provided was 73,649. The CPH location data was provided in easting and northing, however, for some aspects of the data processing, a longitude and latitude value was needed. Converting eastings and northings to latitude and longitude was achieved by importing the data into QGIS version 2.18.3 (QGIS Development Team, 2017) and converting it into a shapefile, then changing the coordinate system from WGS1984 to British National Grid. The data points that had no latitude and longitude were removed from the dataset (0.4%, n=295). Points that were located in the sea were also removed (0.41%, n=304). The statistical software R (R Core Team, 2019) was used to filter out any remaining rows which contained missing data (5.8%, n=4,298). Some of the sheep holdings provided in the data were not farms, but markets. These were identifiable by the CPH 00/000. Markets were removed (0.18%, n=132) and saved for use in later analyses. After all stages of data processing, 68,620 (93%) sheep holdings in England, Wales and Scotland remained in the dataset for inclusion in the spatial model. Summary data for this final data set is provided in Table 3.3.

3.3.3.5 Splitting sheep holdings into regional groups

Nodes were split into regions (Scotland, Northern England, Central England, Eastern England, South West England and Wales) according to Fig. 1 from Bisdorff, et al. (2006), which was imported into QGIS v2.18.3. Georeferencing was used to ensure that the image was at the same Coordinate Referencing System (CRS) as the sheep holding dataset (EPSG:3857 WGS84 pseudo) and the image was used to draw polygons for each region. The clip tool was then used to select the farms from the APHA dataset that were found in each region.

In order to identify which sheep holdings in Scotland were contained within which islands, the Island Groups boundaries shapefiles were downloaded from the National Records of Scotland website (National Records of Scotland, 2011). The clip tool was used for each Scottish island shapefile to select the farms from the APHA dataset that were located in the corresponding Scottish Island.

3.3.3.6 Plotting heatmaps of initial data

The data were used to create a heatmap showing the density of farms in Great Britain using the Heat map (Kernel Density Estimate) interpolation plugin in QGIS v3.03 with a search radius of 10 km and with 1 km^2 grids (Fig. 3.2). The locations of sheep farms were plotted and coloured according to the number of sheep in the farm using the graduated style in the layer properties in QGIS v2.18.3 (Fig. 3.3).

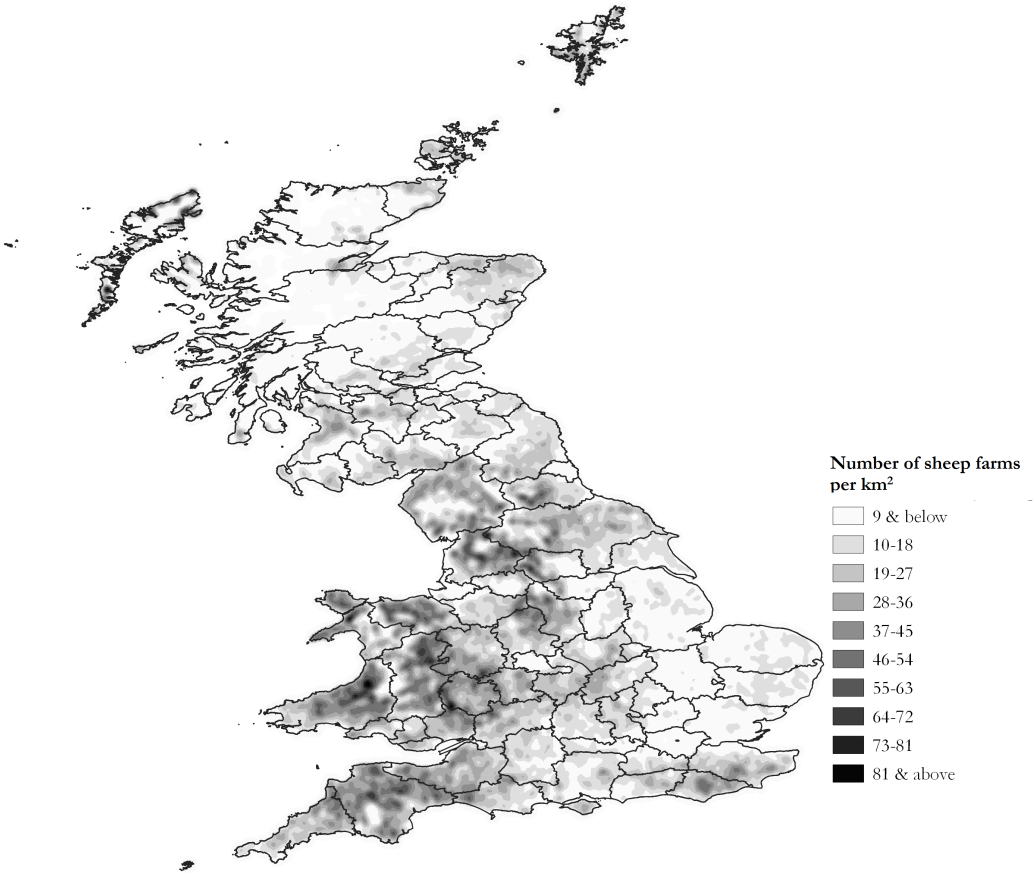


Fig. 3.2 The density of sheep farms in Great Britain per km² with search radius 10km and using Kernel Density methods. Data on the locations of farms and number of sheep per farm were provided by APHA

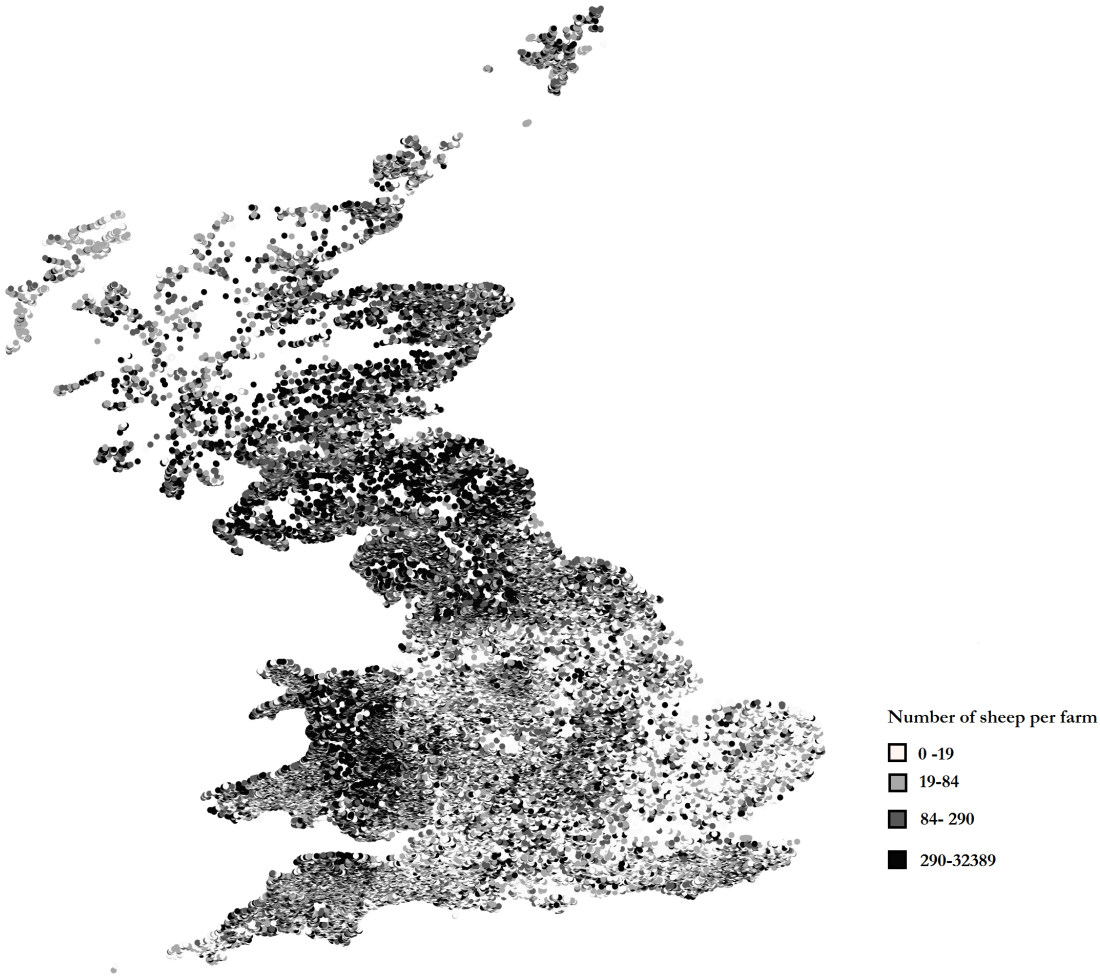


Fig. 3.3 The number of sheep in sheep farms in Great Britain. Each farm is represented by a circle of uniform size, coloured according to the number of sheep in that farm. Data on the locations of farms and number of sheep per farm were provided by APHA

Table 3.3 Number of farms in each country in Great Britain

Country	Number of Farms	Mean number of sheep per farm
England	42480	195
Scotland	14150	293
Wales	11990	384
Great Britain	68620	248

3.3.3.7 Identifying common grazing nodes

As previously mentioned in section 3.3.3.2, in the model a higher mixing rate is used between farms where both use common grazing. The data available to estimate which farms use common grazing were different for each country in Great Britain and so various approaches needed to be employed; these are described separately for each country. In Scotland, it was assumed that the islands were separate units and so farms located on each island were also identified. The categories that were assigned to each farm (common-grazing, island, standard) are shown in Fig. 3.4 and Table 3.4.

3.3.3.7.1 England

The database of registered common land, available on the DEFRA website (DEFRA, 2015), was used to identify where farms were likely to be using common grazing in England. The data points (farms) in common grazing areas that were used for sheep (rather than for other livestock) were selected using R. For these data points, the number of farms with 'Final Rights to Pasture' (max n=545) and 'Provisional Rights to Pasture' (max n = 637) were summed for each common grazing area to find the maximum number of farms that could have rights to pasture on each common grazing area. This assumed that all farms with provisional rights to pasture would have these rights approved and so may be an overestimate.

A distance matrix in QGIS can identify a specific number of points nearest to a polygon. Here, it was used to identify the nearest farms (from the APHA data) to each common grazing area. Each common grazing area has a different number of farms with rights to pasture, however, as the distance matrix only takes one value for the number of points nearest to a polygon, the maximum result across all farms (1,182 rights to pasture for one farm) was used to ensure all farms were selected for each common grazing area. The output from the distance matrix for each common grazing area gave the farms in order of closeness and this output was used in R to select the correct number of farms for each common grazing area. A CRS of EPSG:27700, OSGB 1936/British National Grid was used in QGIS to ensure that

the distance between the common grazing area and the nearest 1,182 farms was calculated in metres.

3.3.3.7.2 Wales

A shapefile of the registered common land in Wales was downloaded from the Lle website which is a data hub provided by the Welsh Government and Natural Resources Wales (Lle, 2014). This had no information about the locations of farms which graze their sheep on the common land and, unlike the dataset used for England, there was no information on the number of farms that use each common grazing area.

In order to find out which farms used the registered common land; a Freedom of Information (FOI) request was sent to each local authority in Wales. In nearly all cases, they were unable to provide this information and the information that was provided was not conclusive. Therefore, survey data was used to estimate how many farms might use common grazing in Wales and the result used to identify which farms use common grazing areas with the assumption that these are the farms nearest to the common grazing areas.

In a 2006 survey of Welsh sheep farmers (n=2,070), it was found that 16.9% of respondents graze their sheep on common ground (Hybu Cig Cymru, 2007) and in a 2016 survey 17.5% (n=170) reported that they used common grazing (Chivers et al., 2018). Hence a value of 16.9% was used here to estimate the number of farms that were likely to use registered common land, since the 2006 survey had a larger sample size.

As described in section 3.3.3.5, the APHA sheep farm dataset was split into regions, one of these being Wales. The sheep farm dataset for Wales contained 12,069 farms, and so using the estimate that 16.9% of these farms were using common grazing gave approximately 2,039 farms. It was assumed that the farms nearest to a common grazing area were most likely to be those that use it. The Geoprocessing toolkit from QGIS was used to create buffers (of various sizes) around the common grazing areas and then select farms (using the "Clip Tool") which are located within the buffers. It was found that a buffer of 705m around all common grazing areas selects 2038 farms

(the closest possible to 2039 and still 16.9% when rounded). The farms selected were therefore assumed to be the common grazing farms in Wales.

3.3.3.7.3 Scotland

As with Wales, FOI requests were sent to local authorities in Scotland to enquire about which farms use common grazing and enquiries were sent to the Crofting Commission. However, no data on the locations of common grazing areas or of farms using them were available and it became clear that common grazing is not defined in the same way in Scotland as in the rest of the UK. Personal communication with a member of the Scottish government's agriculture statistics team revealed that there are multiple arrangements between farmers, where flocks from multiple holdings move to the same areas, but that these areas are often not necessarily officially registered common grazing areas. However, upland farmland is where common grazing usually occurs and, this is generally located in the Severely Disadvantaged Less Favoured Areas (Scottish Government, 2017; National Farmers Union, n.d.). Less Favoured Areas have also been used by the government to define which farms were considered to be "upland" farms in 2010 to 2011 (Parliament UK, 2010) . Therefore, it was assumed that farms within the Severely Disadvantaged Less Favoured Areas would be grazing their sheep together with those from other farms.

An ESRI Shapefile of the Less Favoured Areas (LFA) in Scotland (1997 data) was downloaded (British Government, 2018). The LFA shapefile was categorised into Severely Disadvantaged, Disadvantaged, Outside LFA and NA (not available) and the attribute table was used to select only Severely Disadvantaged. The "Clip Tool" was used to select farms from the APHA data within the severely disadvantaged areas.

3.3.3.8 Identifying Scottish island nodes

The Scottish islands were considered to be separate units from the rest of the farm network and had a different mixing rate to other farms (see section 3.3.3.2). Island group location data for 2011 was downloaded from the National Records of Scotland (Scottish Government, 2019). The shapefile was then separated into multiple shapefiles, one for each island group (including one group that represented

the Scottish mainland), using the "Split Vector Layer" in the Data Management Toolkit. The farms within each island group were selected using the "Clip" tool from the Geoprocessing Toolkit and saved into individual csv files. No farms were located with the shapefiles for Berneray and Easdale and so csv files for these islands were not created.

Table 3.4 The proportion of sheep farms assumed to be using common grazing or to be located on islands in a between-farm model of sheep scab transmission.

Country	% farms in model considered to use common grazing	% farms that are on islands
England	19.6	0
Wales	16.9	0
Scotland	53.7	25.9

Fig. 3.4 The categories of sheep farms used in a between-farm model of sheep scab transmission. These included farms which were assumed to be using common grazing (green) and therefore had a higher between-farm transmission rate compared to normal farms (grey) and farms which were considered to be on an island where complete mixing between all farms could occur (pink).

3.3.3.9 Identifying edges between neighbouring farms

As mentioned previously, it has been suggested that scab can be transmitted between neighbouring farms via mites on wool tags on shared fences, brambles or bushes (Bates, 2007). A network of nodes across Great Britain was created where neighbouring farms were connected by mixing edges.

The average area of a farm in the UK was 84 hectares (or 0.84km^2) in 2010 (Eurostat statistics explained, 2013). Assuming the area of a farm is a circle, then the radius of an average farm with area 0.84km^2 is:

$$r = \sqrt{\frac{840000}{\pi}} \qquad 3.10$$

$$= \sim 517\text{m}$$

Therefore, the diameter of an average farm is ~1.4km and this is also the distance between the centres of two adjoining circular farms (Fig. 3.5).

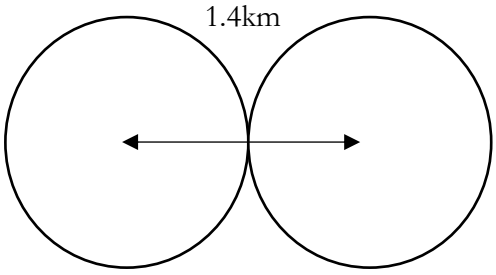


Fig. 3.5 Schematic of average neighbouring sheep farm diameters, assuming both farms are circles

It was assumed that farms could be considered to be neighbours if the location of the centres of the two farms were 2km or less from each other. This decision was taken because farms are not actually circular in shape and because a CPH can cover land and buildings up to 16km away from the main livestock handling area (DEFRA, 2018a), so it was thought that rounding up from 1.4km rather than rounding down would lead to more accurate results. An algorithm was written in the programming

software R that was used to select farms that were less than or equal to 2km away from each other.

3.3.3.10 Mixing rate for edges

Different mixing rates, as specified in section 3.3.3.2 and given in Table 3.1 were used for the corresponding edges. A common grazing edge was considered to be an edge between two farms that both use common grazing. All other edges (with the exception of islands) were non-common grazing edges.

3.3.3.11 Producing the Pajek graph in STEM

The programming software, R, was used to arrange the data into the correct format to be used in a LibreOffice ® file with macros that can be downloaded from the STEM website (Douglas et al., 2018b). The net file produced was then uploaded to STEM and converted to a pajek graph.

3.3.3.12 Calculating the degree distribution of the network

The number of connections each farm had with other farms (degrees) was calculated in R by creating a frequency table of the edges. The nodes that had no edges were added to the dataset so that zero values would be included. The distribution of these results were plotted (Fig. 3.9, Fig. 3.10) and a heat map produced showing the locations and degrees of farms (Fig. 3.11). Another heat map of the same data was produced, but using kernel density estimation, where sheep farm locations were weighted by the degrees (Fig. 3.12), using QGIS v3.03. A quartic kernel shape was used with 1 km^2 pixel grids, a search radius of 10 km and colour shades determined by quantile.

3.3.3.13 Calculating R_0 for the network

The basic reproduction number (R_0) is the average number of secondary cases that result from the introduction of one infected individual into a population of susceptibles (Keeling & Rohani, 2008). Here, the R_0 is calculated at a farm level and so reflects the number of newly infected farms that become infected from contact with one infected farm.

The R_0 of sheep scab between farms in the network was estimated for each farm that uses common grazing ($R_{0_{cgf}}$) using:

$$R_{0_{cgf}} = \left(N_{cg} * \sigma_{cg}\right) + (N_l * \sigma_l) \qquad 3.11.$$

Where N_{cg} is the number of connections with other farms that use common grazing, N_l is the number of connections with other farms that do not use common grazing, σ_{cg} is the mixing rate between farms which both use common grazing ($\sigma_{cg} = 0.5136$) and σ_l is the mixing rate between farms where only one or neither use common grazing ($\sigma_l = 0.01536$, see 3.3.2.2 for how the mixing rates are estimated).

The R_0 of sheep scab between farms which are located on islands ($R0_I$) is calculated as:

$$R_{0_I} = (N_I * \sigma_I) \qquad 3.12$$

Where N_I is the number of connections with other farms on the island and σ_I is the mixing rate between neighbouring farms located on islands ($\sigma_I = 1$). It is assumed that farms on islands can only connect with farms that are located on the same island as themselves.

The R_0 of sheep scab between farms which do not use common grazing and are not located on an island (R_{0_l}) is calculated as follows:

$$R_{0_l} = \left(N_f * \sigma_l\right) \qquad 3.13$$

Where N_f is the number of connections with other farms that either use common grazing or do not use common grazing (farms on islands are not included here).

3.3.4 Experiments

3.3.4.1 Simulation of the 1973 reintroduction of scab in Great Britain

As described in the introduction (3.1), sheep scab was eradicated in Great Britain in the 1950s, however it was reintroduced in late 1972 (Loxam, 1974). After the detection of scab in Great Britain in 1973, a wide range of tracing, dipping and movement restrictions occurred for the following year (Loxam, 1974) and then a range of regional and then national compulsory dipping measures were implemented in the subsequent few years until 1992 where the disease was deregulated (French et al., 1999).

Data on the locations and dates of sheep scab outbreaks in Great Britain from 1973-1992 were taken from two sources:

1. Data for 1973-1982 were taken from the parasitology records from the Ministry of Agriculture, Fisheries and Food (MAFF) Veterinary Laboratories Agency (VLA), Addlestone, UK. The data included the addresses of infected sites and the date at which *P.ovis* infestation was confirmed by skin and wool scraping diagnosis at the MAFF VLA.
2. Data for 1983-1992 were taken from files stored at the MAFF State Veterinary Service, Tolworth, UK. The data included the Ordinance Survey (OS) Grid references of infected sites and the date at which *P.ovis* infestation was confirmed by skin and wool scraping diagnosis at the MAFF VLA.

These sources were drawn from prior to 1999 and the data was collated and tidied by Nigel French, who used this data in his own analyses (French et al., 1999) and provided it for use in this thesis. This data will be referred to as the "MAFF" data throughout this chapter.

A simulation of the model was run, which had the same farms initially infected as in the 1973 reintroduction (Fig. 3.6, Fig. 3.7). This simulation will be referred to as the "1973 Reintroduction Simulation" throughout this chapter. Farms (n=19) that were identified as having an outbreak in January 1973 in the MAFF data were matched to the corresponding farms in the APHA data (Fig. 3.6). This was achieved by identifying which farms were closest in distance between the two datasets, using a distance matrix in QGIS v 2.18.3. The corresponding stem node identifiers in the

network were allocated to each farm using an algorithm in R. These were the farms that were set to be initially infected using an external data initializer in STEM (Kaufman et al., 2019b).

The model was then run for a simulated 10 years, from 1st February 1973 to 31st May 1992, under the standard parameter values specified in Chapter 2. The model was run with 22 unique stochastic seeds. The population in each compartment (Susceptible, Infected, Treated, Dead) at each farm at each time step was recorded using a CSV file logger (Davis & Kaufman, 2016). Initially an equirectangular map logger (Davis & Kaufman, 2016) was used to capture a view of the map every 30 days, from 1st April 1973 to 21st May 1992, however these maps are not presented here.

All simulations were checked to ensure that none had the same stochastic seed, and simulations where the files containing the compartmental data were removed if they were less than 1,000,000kb in size (as this indicates that the simulation did not complete). The last map produced for each simulation run was checked to ensure that the simulation had run for the specified amount of time.

REDACTED FIGURE: SENSITIVE AND IDENTIFIABLE INFORMATION

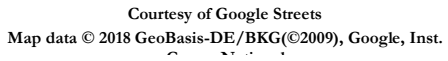


Fig. 3.6 Locations of farms that were known to be infected initially in the 1973 scab reintroduction (MAFF data) and used as initially infected farms in the simulation of sheep scab in Great Britain. The blue markers indicate the locations of these farms in the MAFF data and the pink markers show locations of the corresponding farms in the APHA data. The map is courtesy of Google Streets.

Fig. 3.7 Farms initially infected in the 1973 reintroduction simulation model of between-farm transmission of sheep scab (red diamonds). In the model a different mixing rate was used between farms which both used common grazing (mixing rate = 0.5136, green dots), between farms on Scottish islands (mixing rate = 1, pink dots) and between normal farms (mixing rate =0.05136, grey dots).

3.3.4.2 Introducing scab into the South West of England

The model was also run under the same conditions but with the initial farms infected in a different location, to allow for comparison. The South West of England was selected because this area had a similar proportion of common grazing farms to the area where farms were initially infected in the 1973 reintroduction simulation. This version of the model will be referred to as the "South West Simulation". For this, 19 farms in Devon were selected at random using the sample() function in base R (Fig. 3.8). Six of these were farms that used common grazing and the remaining 13 did not. The model was run with 10 repeats, each with a different stochastic seed, over the same time period and with the same conditions and parameters as the 1973 Reintroduction Simulation.

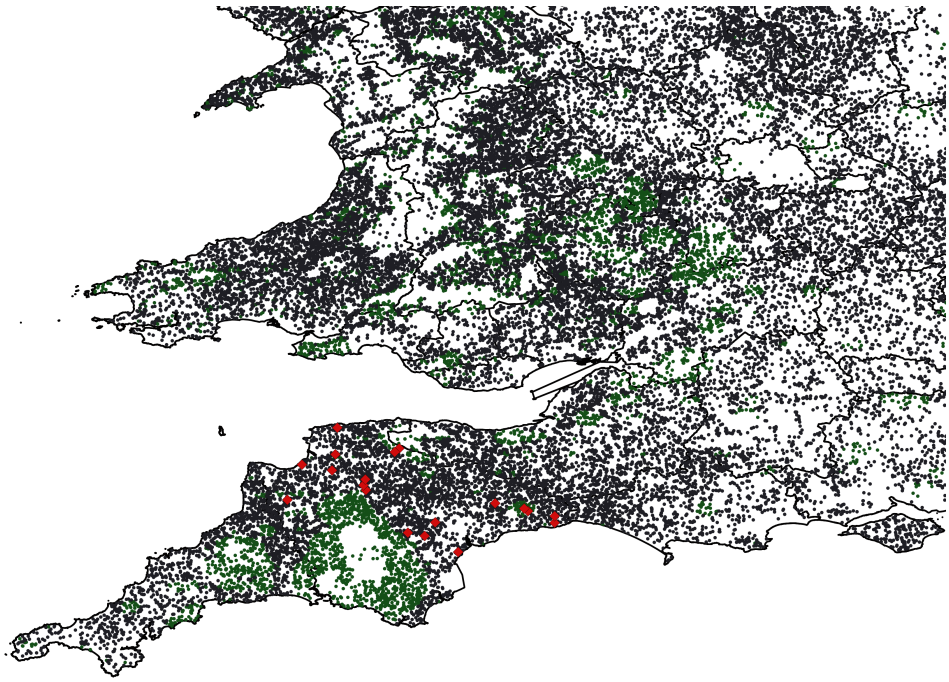


Fig. 3.8 Randomly selected sheep farms in Devon (red diamonds, n=19) to be used as initial index cases in the South West simulation of between-farm transmission across Great Britain. Other farms shown are those which use common grazing (green) and those which don't (grey).

3.4 RESULTS AND DISCUSSION

Although there have been studies that have looked at the network of movements of sheep between farms (Kiss et al., 2006; Kao et al., 2007; Volkova et al., 2010) and cattle (Robinson et al., 2007) due to buying and selling, as far as the author is aware, there have been no studies that have developed a metapopulation model for sheep disease transmission via purely farm-to-farm contact in Great Britain.

3.4.1 Network of neighbouring farms

There were 2,395 farms that did not connect to any other farms in the network (Fig. 3.9). The majority of farms had less than twenty connections with other farms and 4 connections was the mode (Fig. 3.9). The mode number of connections in Scotland (3) was lower than for England (4) and Wales (9) and the majority of farms in Scotland had less than 13 connections, however, unlike England and Wales there were some farms that had more than 40 connections (Fig. 3.10). The maximum number of connections any one farm had to other farms was 83. This farm was located on South Uist, an island in the Outer Hebrides of Scotland. The other farms on this island also had a similar number of connections (~80) (Fig. 3.9, Fig. 3.10).

The network of subpopulations developed in this chapter suggests that there are regions of Great Britain where there are highly clustered groups of sheep farms between which sheep scab may be transmitting via neighbour-to-neighbour contact. The regions in Great Britain where farms have the highest degrees (number of connections between them) are Wales, South West England, some areas of Northern England and South East England and some Scottish islands (Fig. 3.11 and Fig. 3.12). Some of these areas correspond with areas where there are a high density of farms using common grazing (Fig. 3.13). Therefore, the spread of sheep scab between these highly connected farms which use common grazing is likely to be very quick.

This is reflected in the results for the R_0 values for farms (Fig. 3.14) which were calculated using the degree distribution and the different mixing rates for farms which use common grazing and those which do not (see section 3.3.3.13). When R_0 is less than 1, each infected case is not able to reproduce itself and the disease will die

out, however, if it is greater than 1 then an outbreak will occur (Anderson & May, 1991). If R_0 is greater than approximately 5, then >99% of a well-mixed population is likely to contract the disease (Keeling & Rohani, 2008). Therefore, Fig. 3.14, gives an indication of which farms, if infected with scab, are likely to cause an outbreak in their area, those which are at a very low risk of causing an outbreak and those which are very high risk. When planning future control strategies, it could be useful to target the high and medium risk farms indicated by Fig. 3.14, or the regions indicated by Fig. 3.12, as this is most likely to more effectively reduce the number of cases and prevent further outbreaks (assuming no long-distance movements are occurring). Some of the high risk regions identified in England here have also been found in previous studies to be high risk areas for scab (Rose, 2011), however the areas highlighted in this chapter are not restricted by human-defined boundaries (they cover the whole of Great Britain) and are more specific than those identified by Rose (2011).

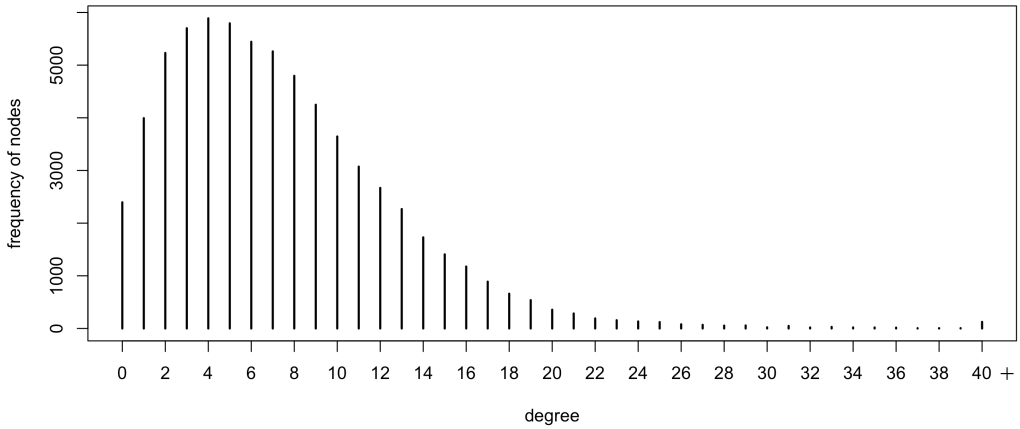


Fig. 3.9 Degree distribution for a network of sheep farms across Great Britain where neighbouring farms are connected by an edge if they are located less than or equal to 2km apart. The degree of a farm is the number of connections it has to other farms. All nodes that had greater than or equal to 40 connections are shown as 40+.

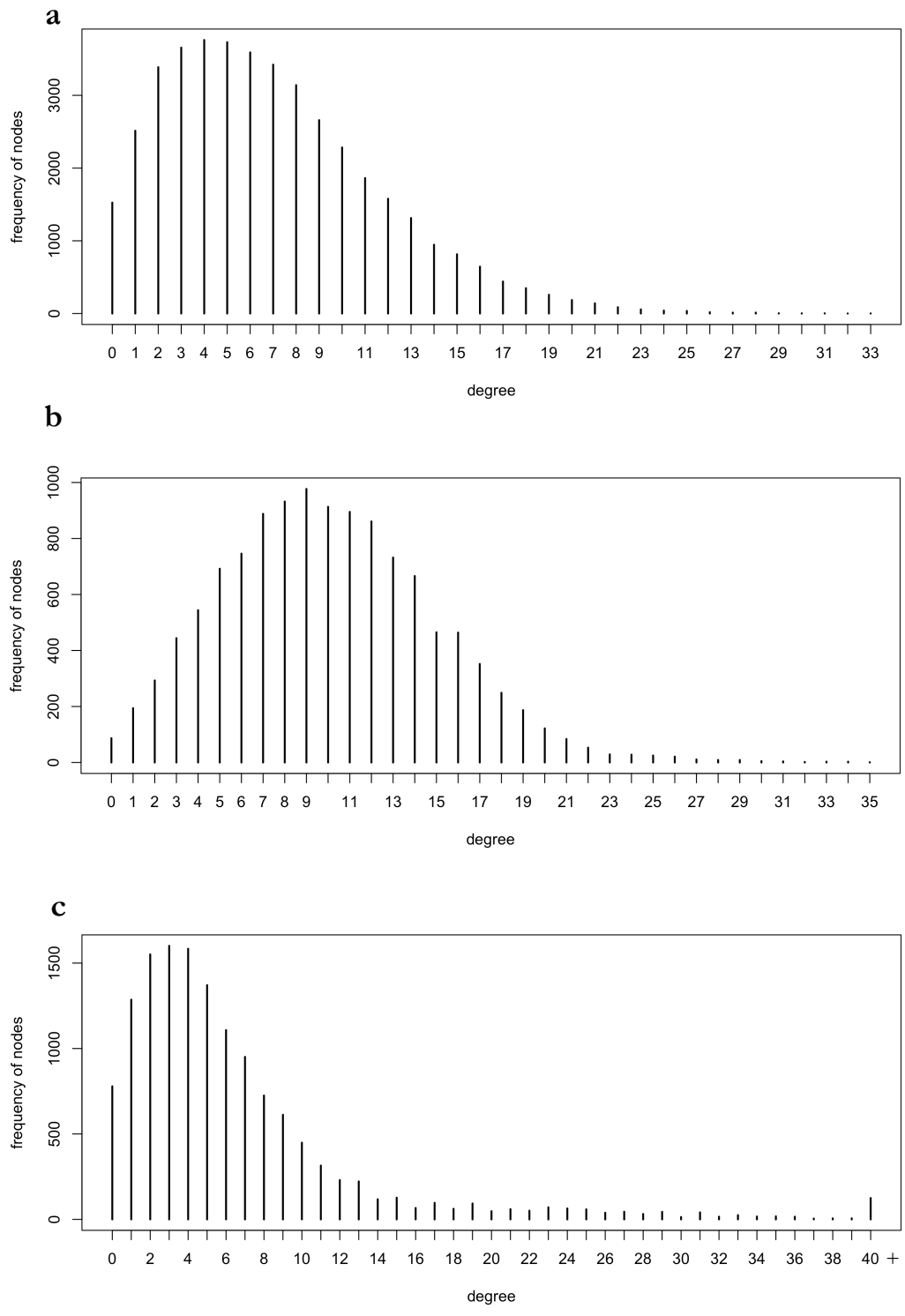


Figure 3.10 Degree distribution for a network of sheep farms across Great Britain where neighbouring farms are connected by an edge if they are located less than or equal to 2km apart. (a) England **(b)** Wales **(c)** Scotland. The degree of a farm is the number of connections it has to other farms. All nodes that had greater than or equal to 40 connections are shown as 40+.

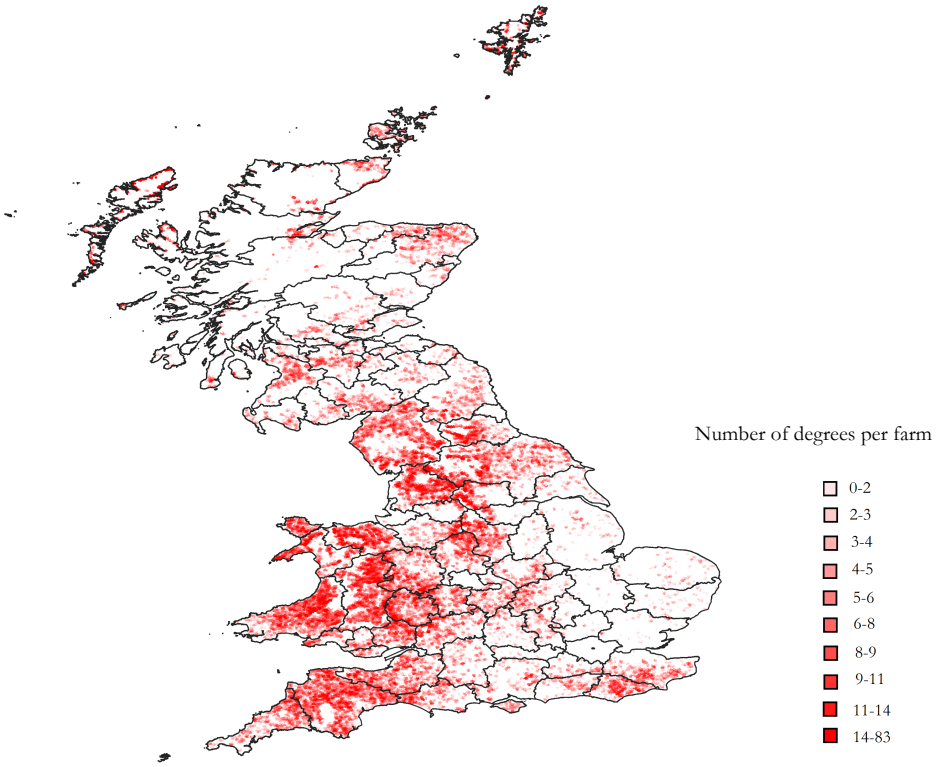


Fig. 3.11 The number of connections (degrees) between sheep farms in a network of neighbour-neighbour (within 2km) contact across Great Britain. Each farm is represented by a circle of uniform size, coloured according to the number of connections it has with neighbouring farms.

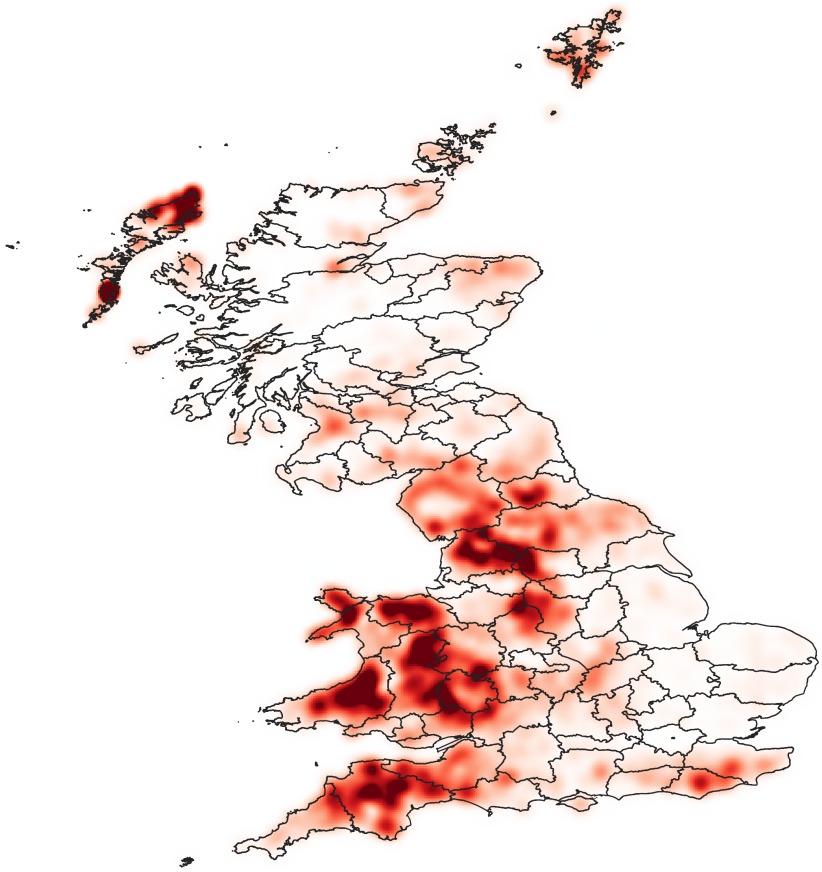


Fig. 3.12 The density of sheep farms weighted by the number of connections between them. The darker the shading, the higher the density of farms and number of connections. This was produced using a Kernel density estimate of sheep farm locations weighted by degree (connections with neighbouring farms) with 1km^2 grids, with quartic kernel shape, a search radius of 10km and colour shades determined by quantile.

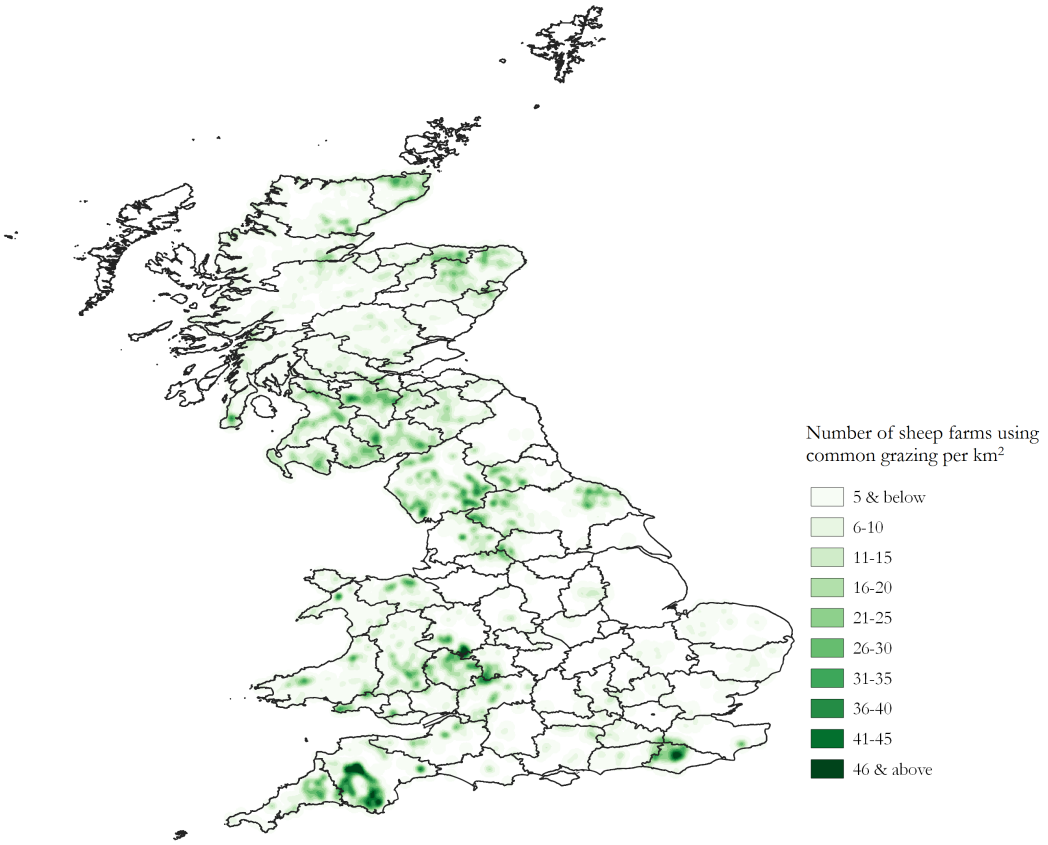


Fig. 3.13 The density of sheep farms considered to be using common grazing in Great Britain as described in 3.3.3.7. The darker the colour, the higher the density of farms that use common grazing.

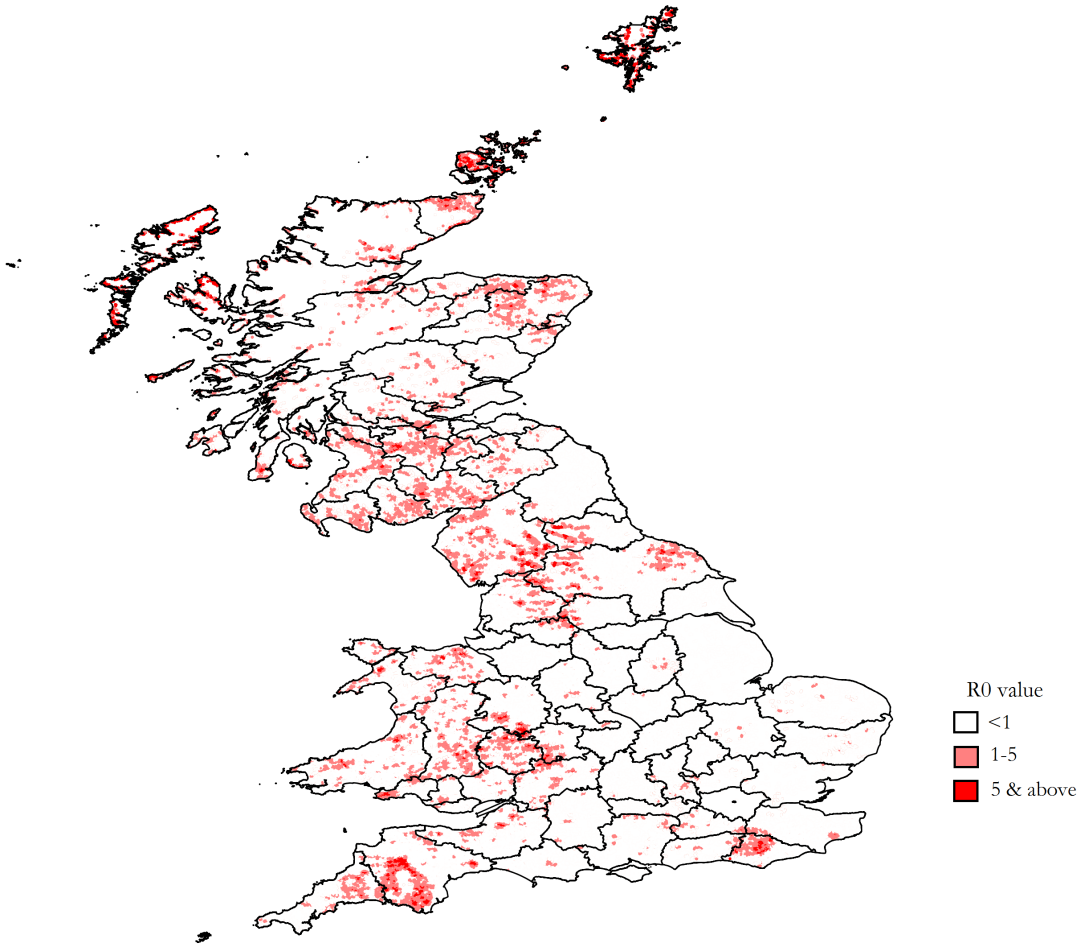


Fig. 3.14 The R_0 values for each sheep farm in a network of neighbour-neighbour contact where contact is assumed between farms within a 2km radius of each other. The R_0 values were calculated as described in 3.3.3.13

3.4.2 Number and locations of sheep farms infected over time in the 1973 reintroduction simulation

Across the 19 years of the simulation of the reintroduction, the number of infected farms increased rapidly after the initial introduction of scab in 1973, then became stable near the end of 1975 (Fig. 3.15). For the following 16 years, the number of infected farms remained fairly constant, at just below 30%, although started to slowly reduce in number after 1982, with a prevalence at around 27.5% in 1992 (Fig. 3.15). No reported prevalence data is available at the time period simulated for comparison; however, incidence data is available and comparison of the simulation results with this is carried out in 3.4.3.

The sheep farms infected over time were generally located in the same counties across all simulation runs (Fig. 3.16). From looking at the spatial spread of scab, it seems that this initial sharp increase in prevalence, followed by a fairly constant prevalence could be explained by spatial dynamics. The results showing the monthly densities of sheep-scab infested farms in the 1973 reintroduction simulation (Fig. 3.17), taken in light of the heat map of (the number of connections) between farms (Fig. 3.12), common grazing farms (Fig. 3.13) and R_0 values for farms (Fig. 3.14) suggests that the sharp increase in prevalence seen in the first few years of the simulation could be related to the fact that the initially infected farms were infested in an area where there was a high density of sheep farms, with high connectivity, a high R_0 and where common grazing is practiced. The limiting factor to prevalence increase after these first few years is likely to be due to the disease having reached the edges of these farm network clusters.

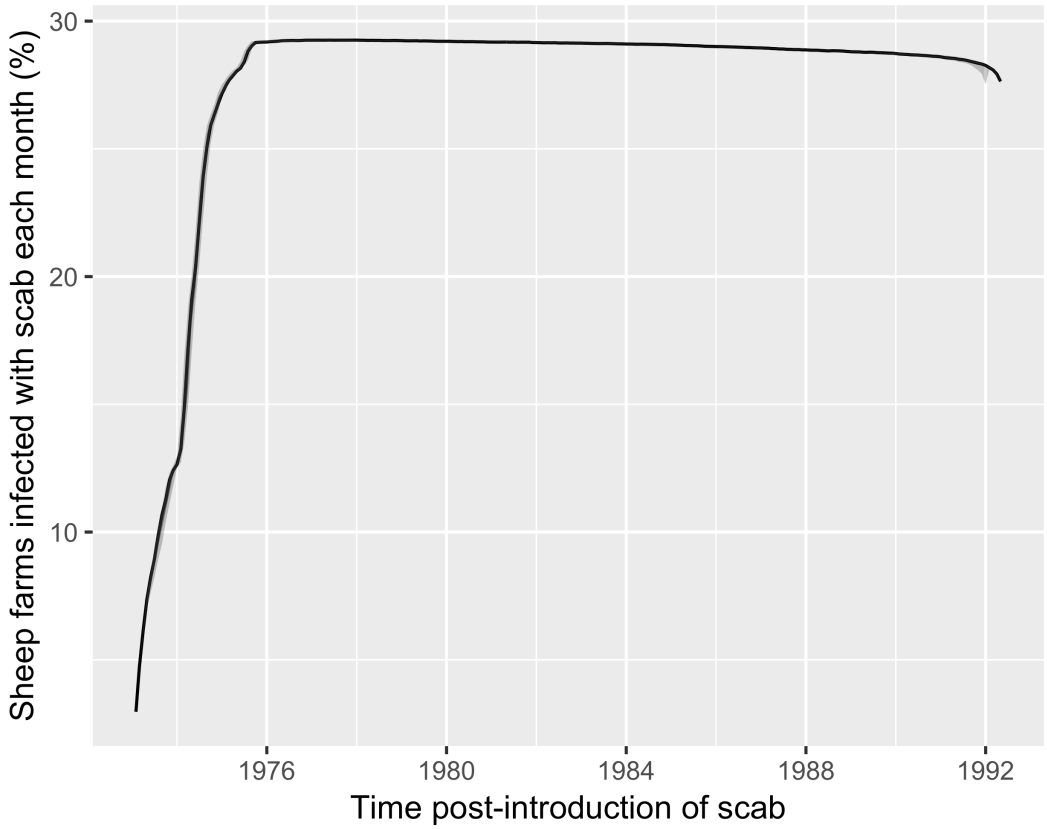


Fig. 3.15 The percentage of farms infested with sheep scab in Great Britain over time, following the simulated reintroduction of sheep scab into 19 farms in Northern England in January 1973 in a between-farm transmission model of sheep scab. The median result (black line), the interquartile range (dark grey shading) and the 2.5-97.5 percentiles (light grey shading) are given for repeated stochastic simulation runs (n=10). The total number of sheep farms is 68,620.

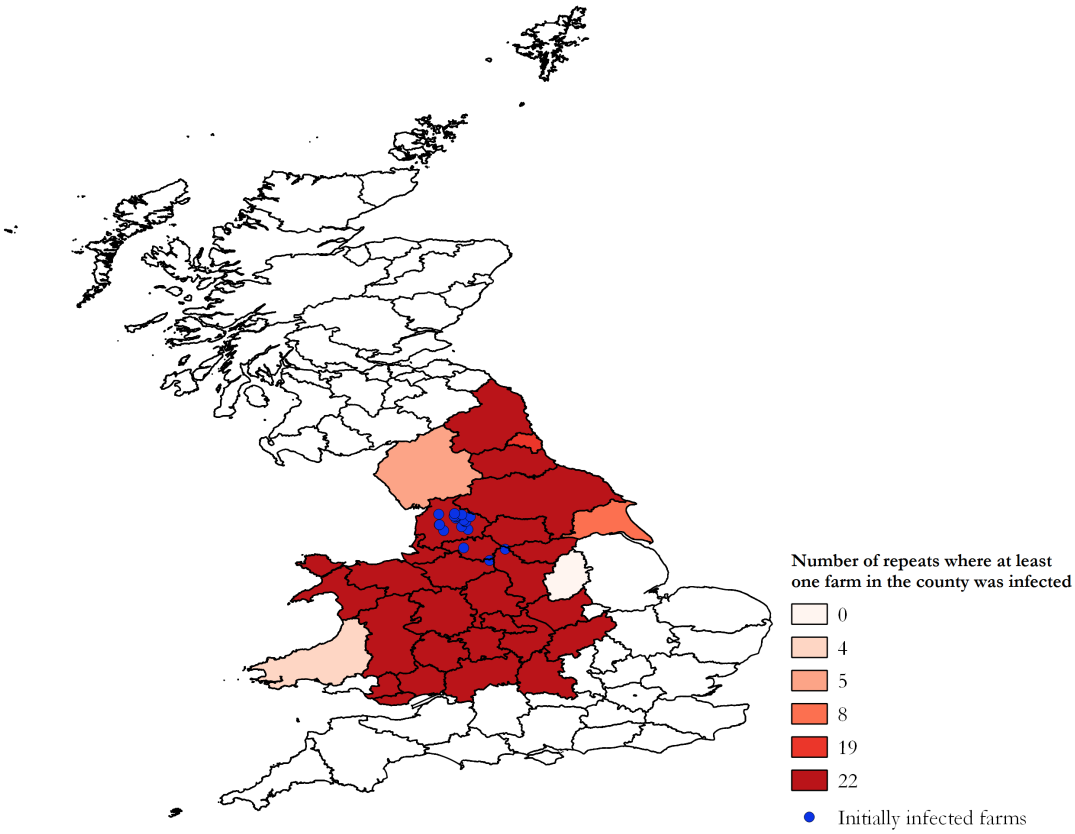
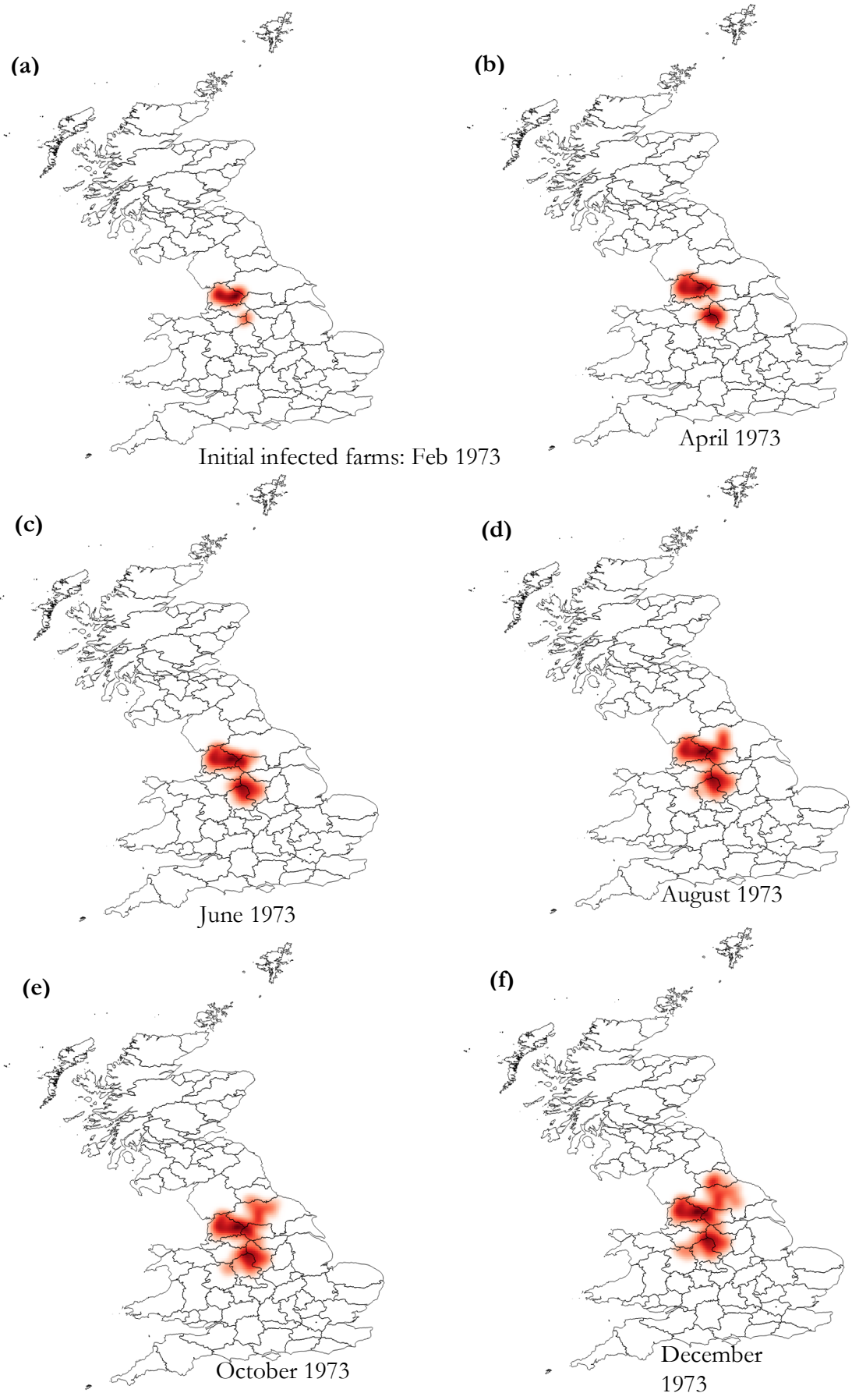
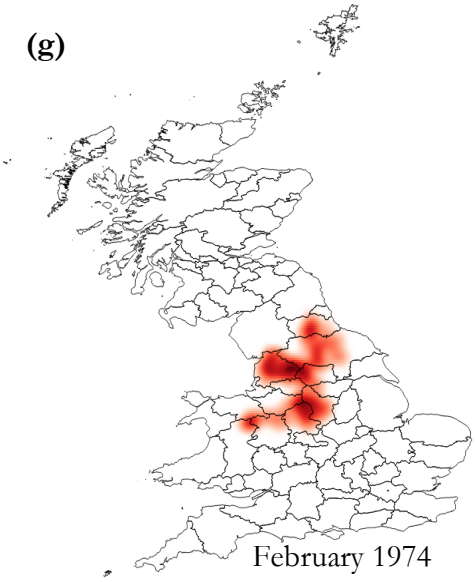
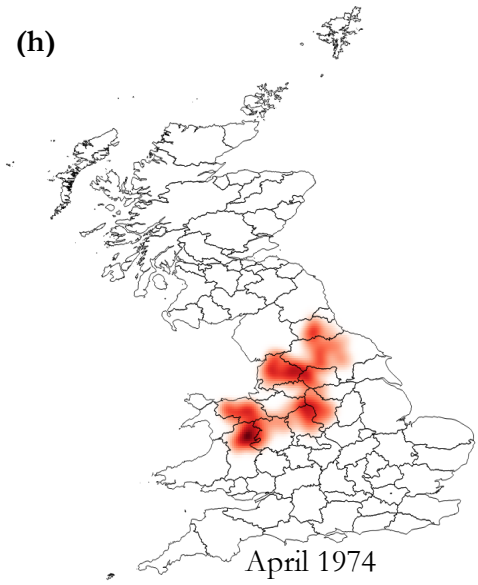


Fig. 3.16 The frequency of having at least one sheep-scab infected farm per county across 22 stochastic repeats on the 27th January 1992 (the last simulation date) in the 1973 reintroduction simulation. The initially infected farms (blue dots) were the same as those seen in the reported results at the time. It was assumed that no treatment for sheep scab was used to prevent or treat scab and that transmission only occurred between neighbouring farms.


(a)
(b)
Initial infected farms: Feb 1973
April 1973
(c)
(d)
June 1973
August 1973
(e)
(f)
October 1973
December
1973


(g)
February 1974


(h)
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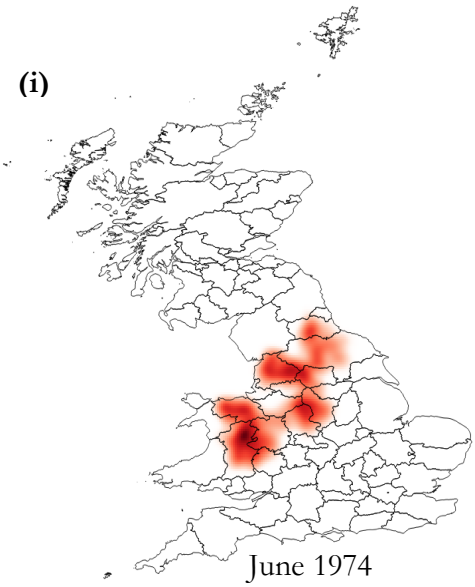
(i)
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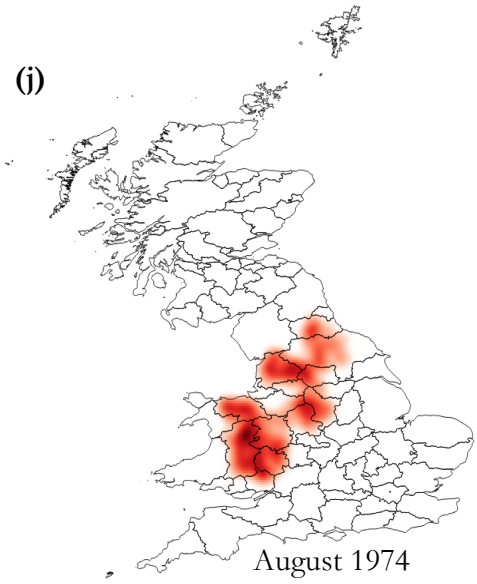
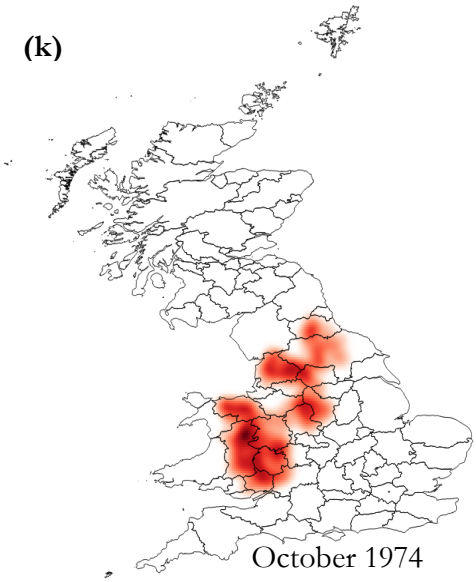
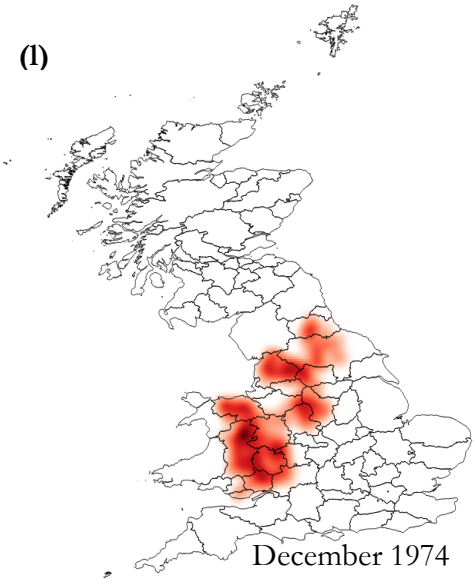
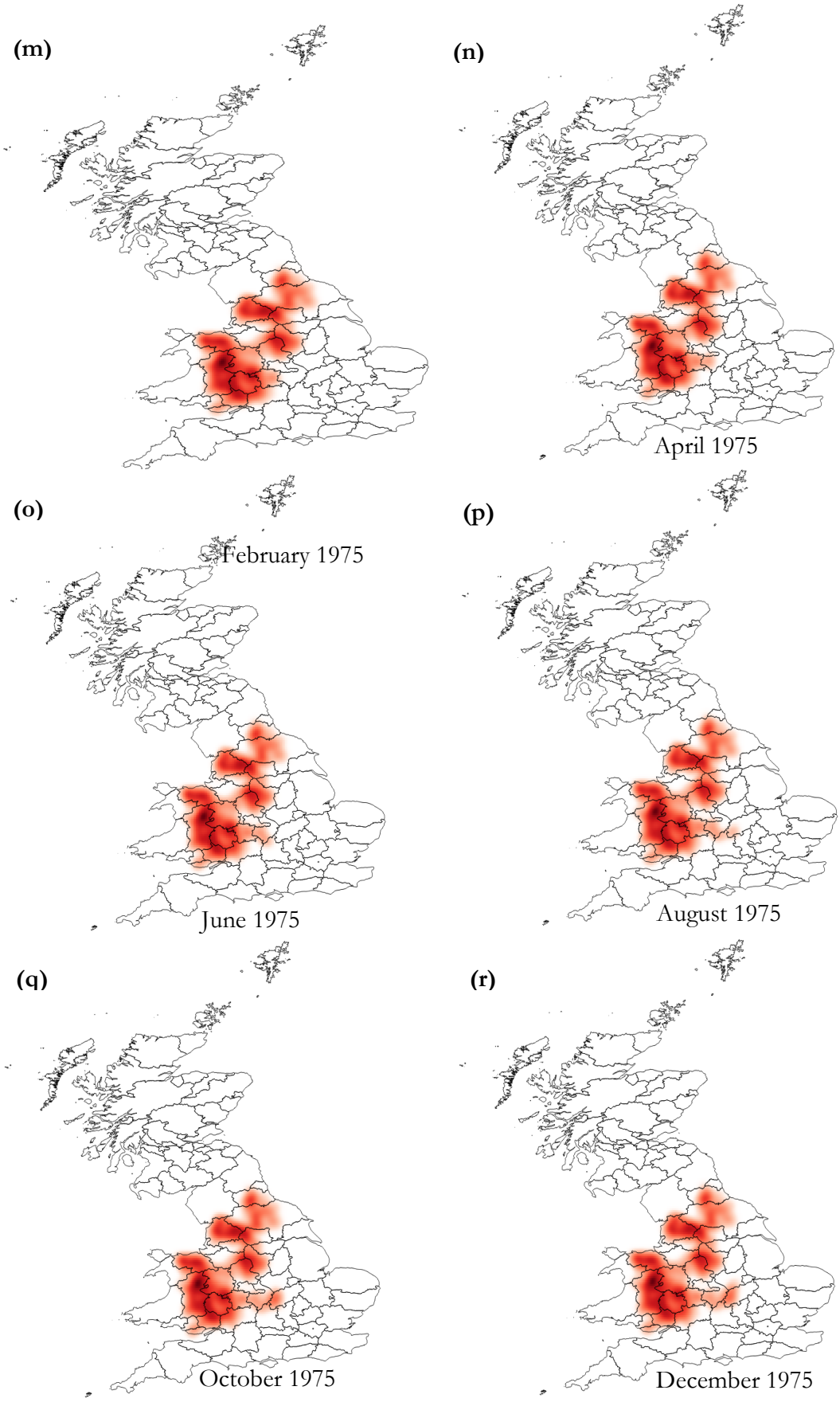

(j)
August 1974

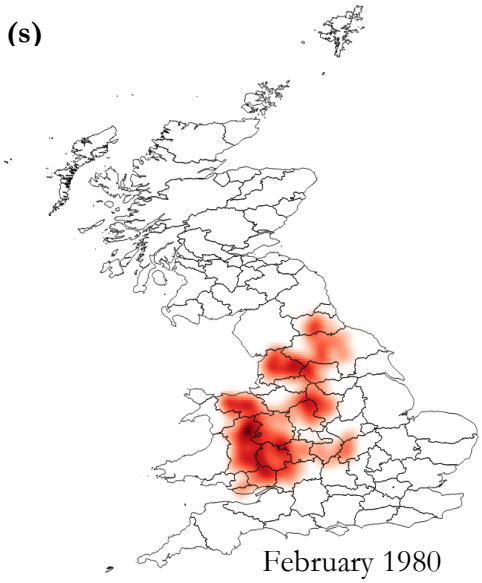

(k)
October 1974


(l)
December 1974



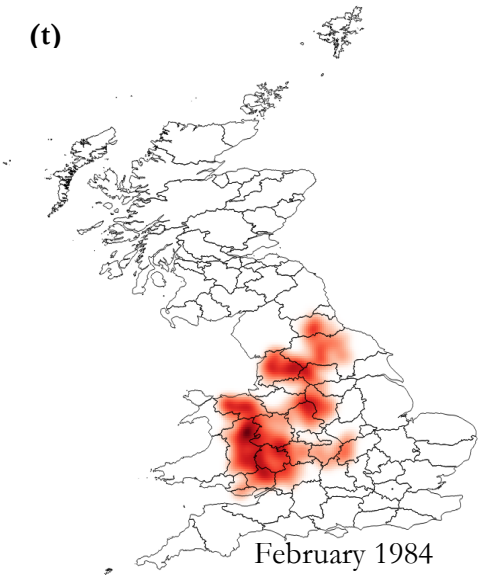
December 1975

(s)



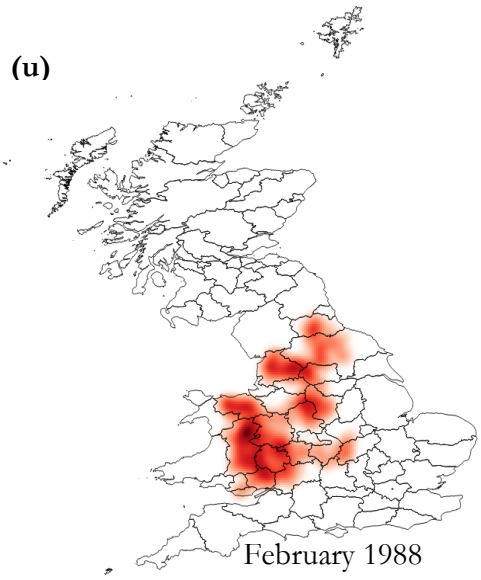
February 1980

(t)



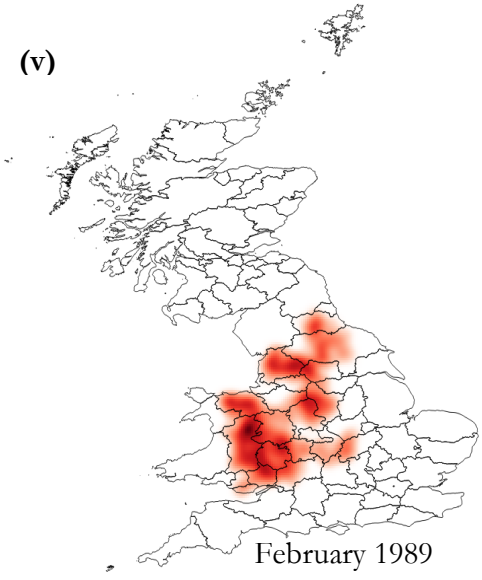
February 1984

(u)



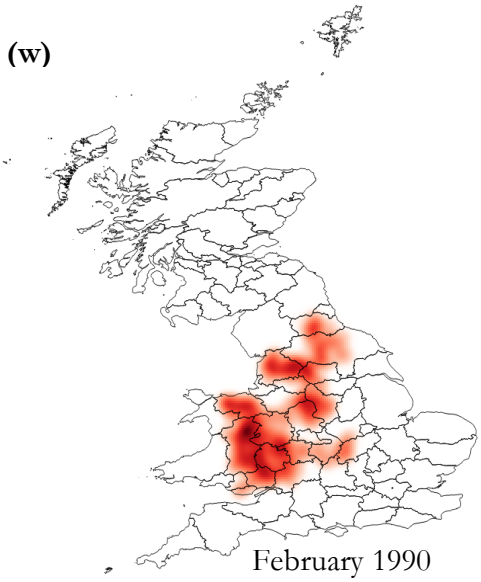
February 1988

(v)



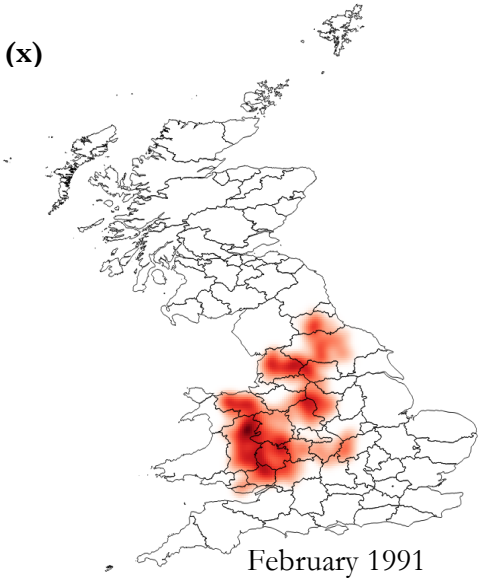
February 1989

(w)



February 1990

(x)



February 1991

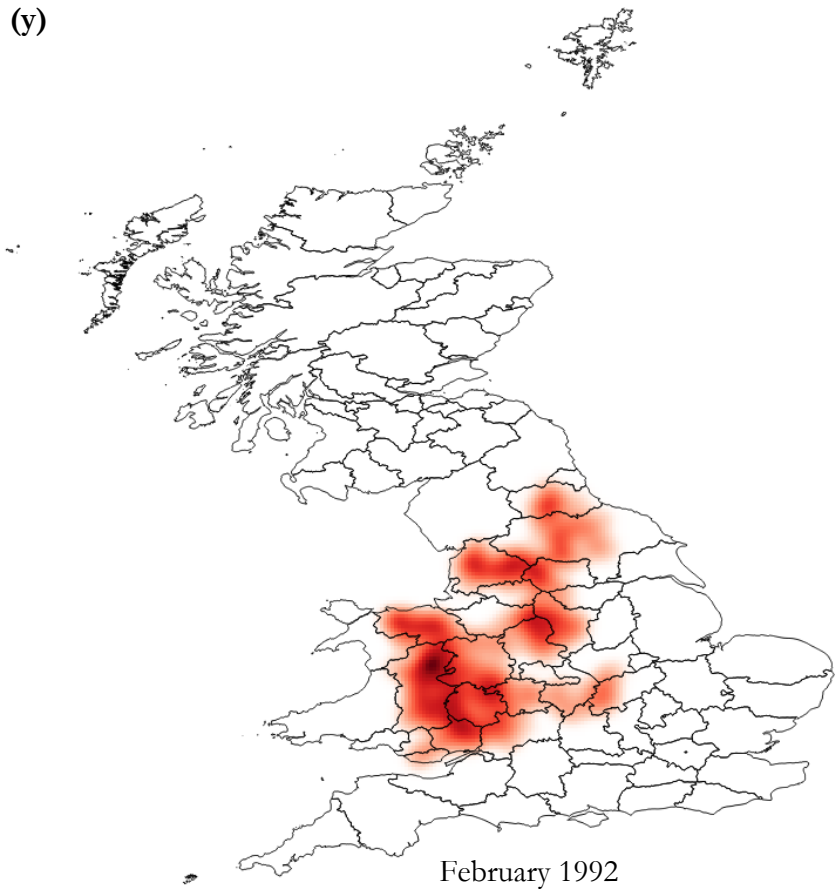


Fig. 3.17 (a-r) Monthly densities of sheep-scab- infected farms in 1973-1975 (s-y) Monthly densities of sheep-scab- infected farms in February of significant years (according to Fig. 3.15 and Fig. 3.18). These results are from one randomly selected run of a simulation of the 1973 reintroduction of sheep scab in Great Britain. The darker the shade of red, the higher the density of infected farms.

3.4.3 Comparison of 1973 Reintroduction Simulation incidence results with reported cases

So far, the cumulative results for incidence (the prevalence of scab) in the model when no treatment is used have been discussed. The MAFF data just reports new cases (incidence), however, it is unknown when, if or how these cases were treated, nor the frequency of unreported cases and therefore this data cannot give an accurate representation of the prevalence of scab during this time. Therefore, the incidence results have also been presented spatially for one randomly selected run of the model, alongside with MAFF data from the corresponding years, to allow for comparison (Fig. 3.20, Fig. 3.21, Fig. 3.22, Fig. 3.23, Fig. 3.24, Fig. 3.25, Fig. 3.26, Fig. 3.27, Fig. 3.28, Fig. 3.29).

When comparing the reported data with the model simulation data, it is important to be aware of the differences between these datasets. In the simulation, it was assumed that no treatment was used, while in reality various control methods were used to prevent and treat scab (French et al., 1999). In addition, in the simulation, sheep were only able to contract scab from neighbouring farms and by using common grazing, whereas, in reality they are also able to contract scab from buying in sheep with scab, strays, contact at markets and through fomites and equipment (Henderson, 1990; van den Broek & Huntley, 2003b). In addition, there may be a lag between the dates where a farm is considered to be infected in the model simulation (when at least one sheep is infected) and in the reported data. This is because the reported data gives the date at which sheep scab was confirmed in a flock, prior to which clinical symptoms must be noticed. Alternatively, in the model, as soon as a sheep is infected, then this is recorded. These three factors: differences in control methods, no long-distance movements and the time lag between incidence and reporting are thought to explain most of the major differences between the model results and the results from reality.

Due to these differences between the model conditions and the data, a full comparison of the model results and the MAFF data is not done here. The spatial patterns are compared visually, and some quantitative results are given. In Chapter 5, an alternative metapopulation model of scab which includes treatment and long-

distance movements is fitted to the MAFF data using Approximate Bayesian Computation.

In the 1973 Reintroduction Simulation, there were initially around 2,000 new cases per month, however, this then decreased sharply throughout 1973 and oscillated around 1,000 cases per month (Fig. 3.18). From 1974 onwards it increased again and then increased more slowly from 1976 to 1992, where there were around 4,000 new outbreaks per day (Fig. 3.18). Looking at the spatial dynamics of the newly infected farms, it seems that the initial increase in 1973 may have happened as the disease spread rapidly through from the initial infected farms to neighbouring farms (Fig. 3.20b), but then the number of new cases decreased until the disease reached Wales in 1974 (Fig. 3.21b). The number of newly infected cases then increased from 1974 onwards since Wales has a high density of farms with a high connectivity (Fig. 3.12), with lots of farms using common grazing (Fig. 3.13) and many farms with a high R_0 (Fig. 3.14).

For the remaining years, the spatial location of new cases remained fairly constant in the same regions (Fig. 3.22, Fig. 3.23, Fig. 3.24, Fig. 3.25, Fig. 3.27, Fig. 3.28, Fig. 3.29), suggesting that the same farms recovered and became re-infected, which is consistent with survey data (Rose & Wall, 2012). It is interesting to note that the number of cases increased slightly over the remaining years of the simulation (Fig. 3.18), while the overall number of infected farms decreased slightly over this same time period (Fig. 3.15). As the spatial data suggests that the location of infected farms remains the same, this pattern is again likely to be due to farms recovering and then becoming re-infected. It seems that at this later time step, the number of farms recovering from scab was slightly greater than the number of new cases that occurred. It would be interesting to see if scab would ever die-out completely without treatment, if longer time series were run in the simulation.

The spatial transmission in the MAFF data did not appear to follow the same pattern as the simulation data, with MAFF cases being more dispersed and seeming to be less associated with the spatial clusters of farms with high connectivity (Figs. 3.20-3.29). This is assumed to be due to the lack of long-distance movements in the model simulation and implies that these may be important for spatial transmission dynamics. There were cases present in the same counties in the same year in the simulation as in the MAFF data in 27.9% of instances (the number of cases per

county per year are given for the MAFF data and for the randomly selected simulation data in the appendix).

On comparing the quantitative model incidence results (Fig. 3.18) to the MAFF data on reported cases from 1973 to 1992 (Fig. 3.19), there are some clear differences. Firstly, the number of new cases is much higher in the simulated results, with the number of monthly reports of scab in the MAFF data never reaching much higher than 60 but ranging from around 1000 to 4000 in the simulation. As explained previously, this difference is likely to be down to the fact that no control methods were used in the simulation, that long-distance movements were not included and because there is likely to be a time-lag between the model results and the reported results. In future a partially observed Markov process could be used to compare the model results to the reported results to try and correct for the time-lag.

Another difference between the model results and the outbreak data is that although there are small fluctuations in the model results, the general trend is a positive correlation between time and number of farms infected (Fig. 3.18), while in the outbreak data the general trend was fairly flat, with seasonal fluctuations, where more cases were reported over the winter months than in other seasons (Fig. 3.19). As described fully in Chapter 1, higher numbers of sheep scab cases have historically been reported in the winter months (Kirkwood, 1986; Bates, 1997b; French et al., 1999; O'Brien, 1999), which has been thought to be due to environmental conditions, timings of sheep scab treatments, autumn sales, changes in stocking density, poorer condition of pregnant ewes and births of lambs. In the model, none of these factors were taken into account (although treatment is included in the Chapter 5 model simulations). In future, a seasonal bias assumed to include the impact of all these factors could be included in the model to more accurately estimate the transmission patterns. Alternatively, some of these factors could be added individually and their impact on the seasonality of sheep scab dynamics measured. On the other hand, if the model is to be used to simulate long-term prevalence patterns, seasonal fluctuations may not be important and might be safely ignored.

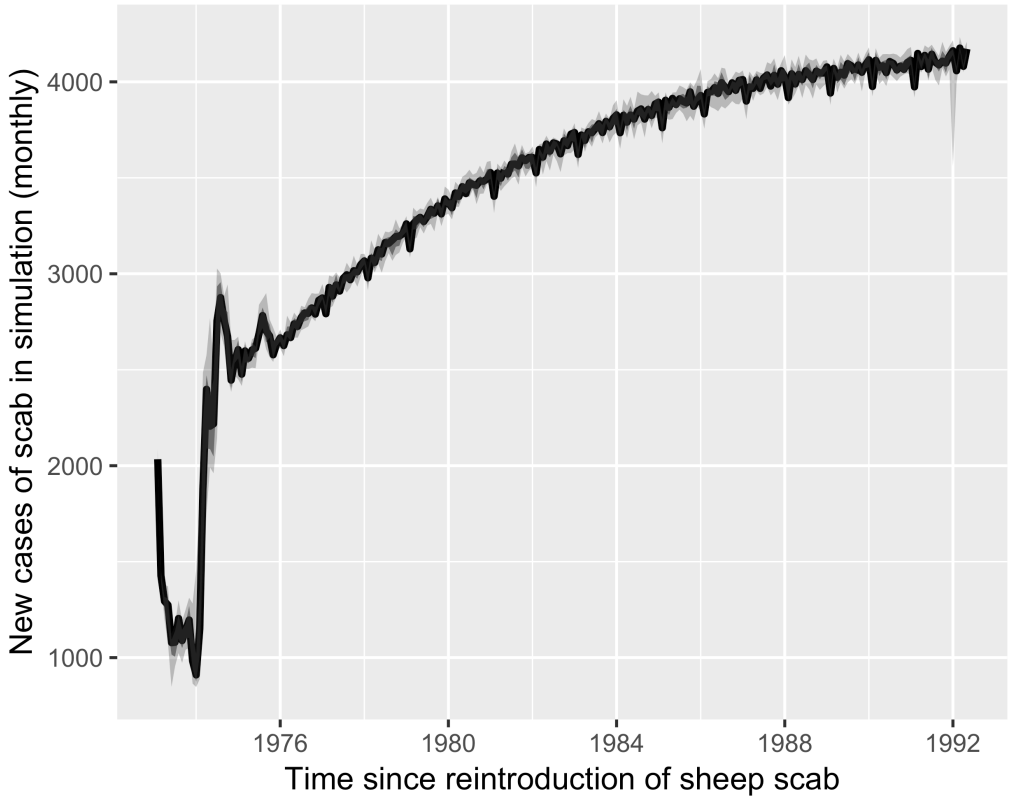


Fig. 3.18 The monthly incidence of farms with scab in Great Britain in a between-farm transmission model of sheep scab from 1st February 1973 to 31st May 1992 (simulated time) where 19 farms in Northern England are initially infected. The median result (black line), the interquartile range (dark grey shading) and the 2.5-97.5th percentiles (light grey shading) are given for repeated stochastic simulation runs (n=10). The total number of sheep farms is 68,620.

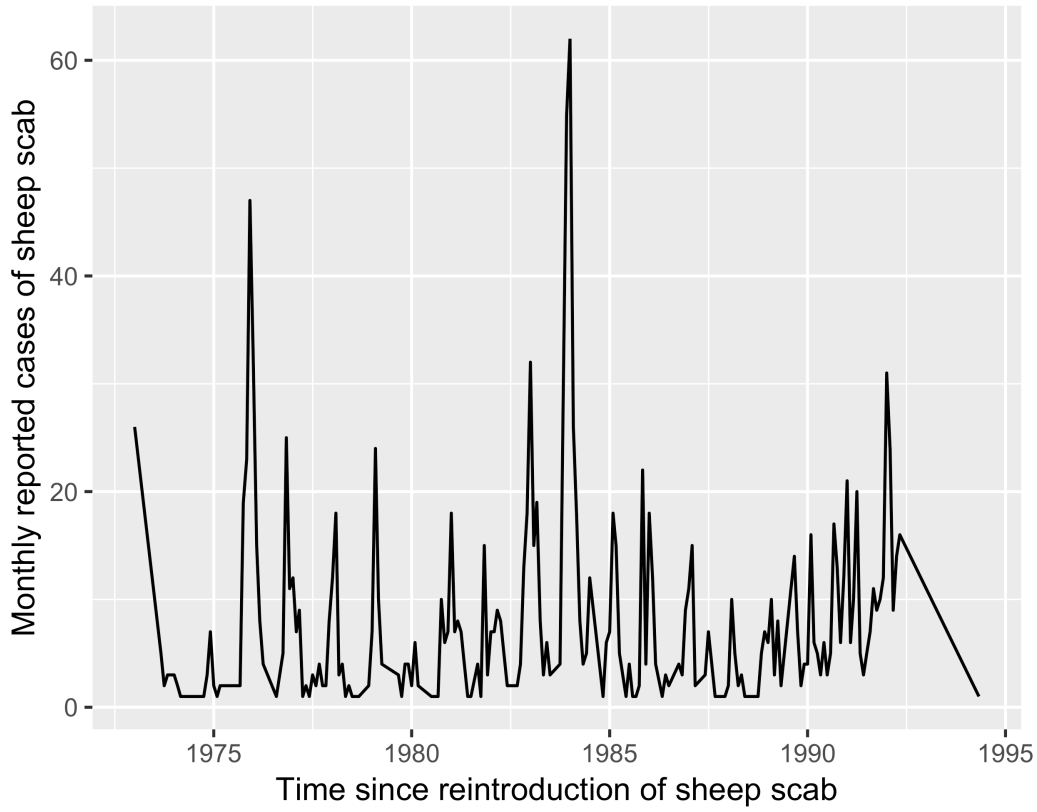


Fig. 3.19 The monthly reported cases of sheep scab in Great Britain from 1st January 1973 to 31st May 1992 according to the MAFF data (full details of this data source explained in 3.3.4.1).

Fig. 3.20 (a) Reported cases of sheep scab in Great Britain in 1973 (b) Incidence of sheep scab in 1973 in the 1973 reintroduction simulation. The darker the shade of red, the higher the density of infected farms.

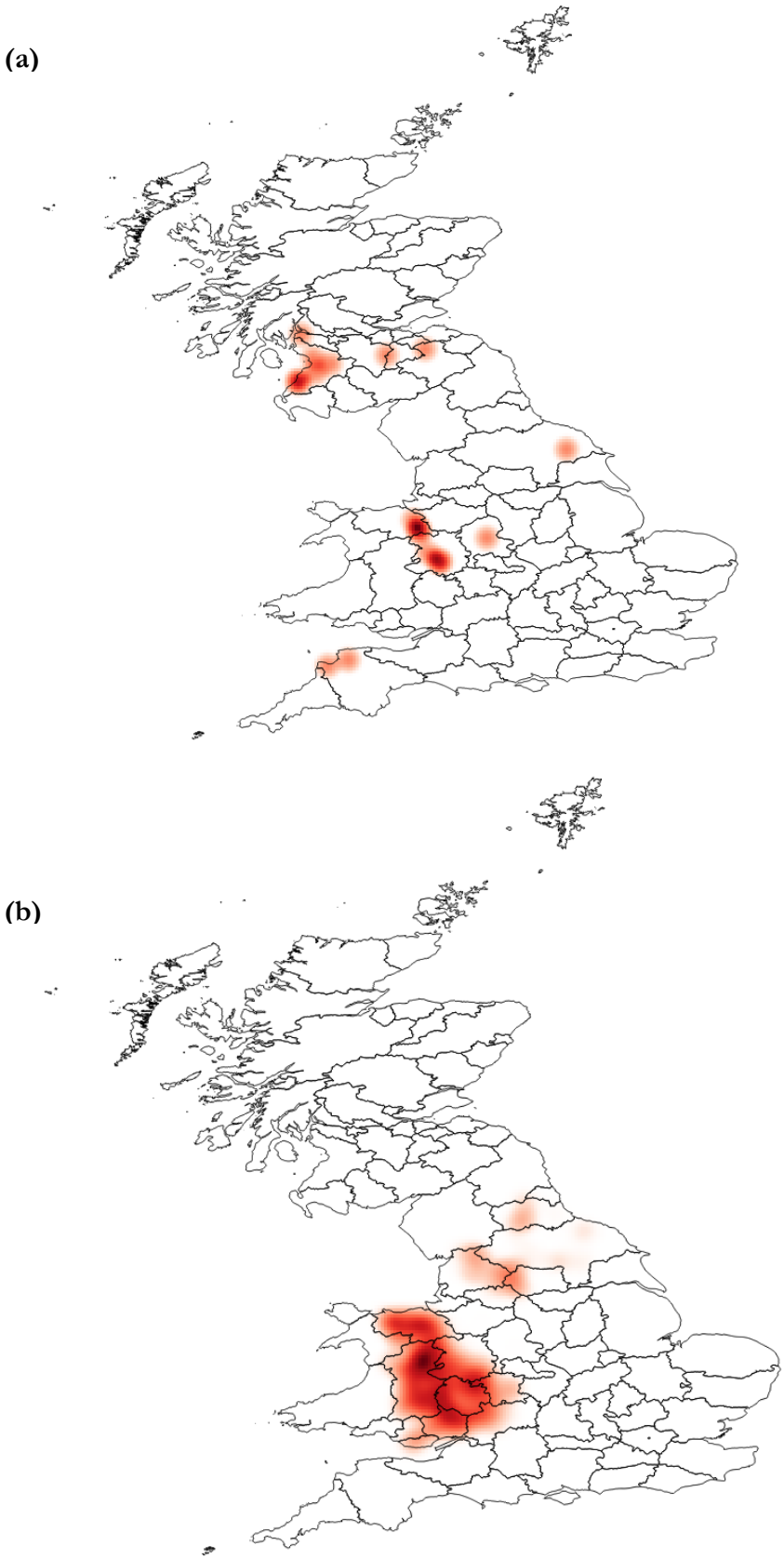


Fig. 3.21 (a) Reported cases of sheep scab in Great Britain in 1974 (b) Incidence of sheep scab in 1974 in the 1973 reintroduction simulation. The darker the shade of red, the higher the density of infected farms.

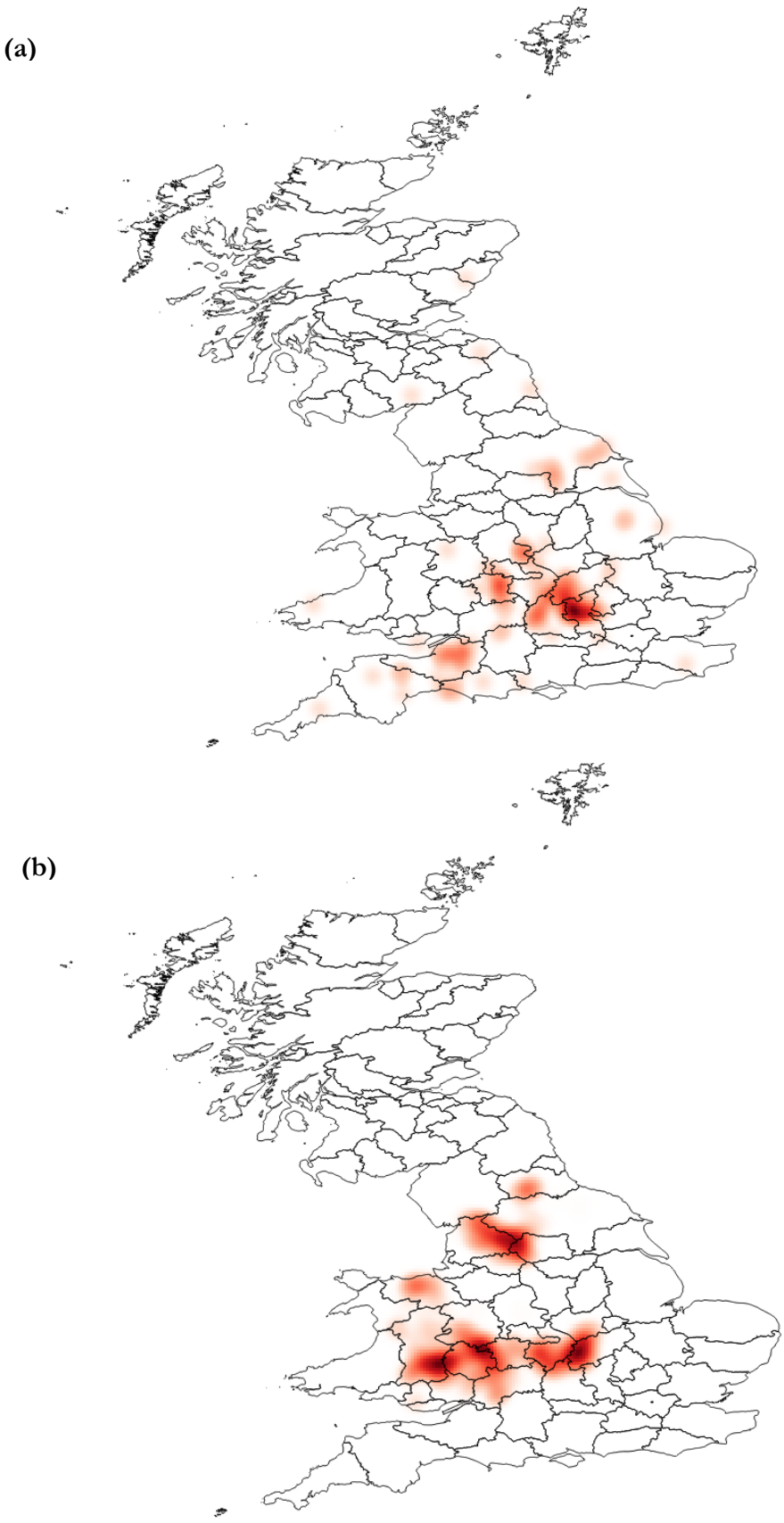


Fig. 3.22(a) Reported cases of sheep scab in Great Britain in 1975 (b) Incidence of sheep scab in 1975 in the 1973 reintroduction simulation. The darker the shade of red, the higher the density of infected farms.

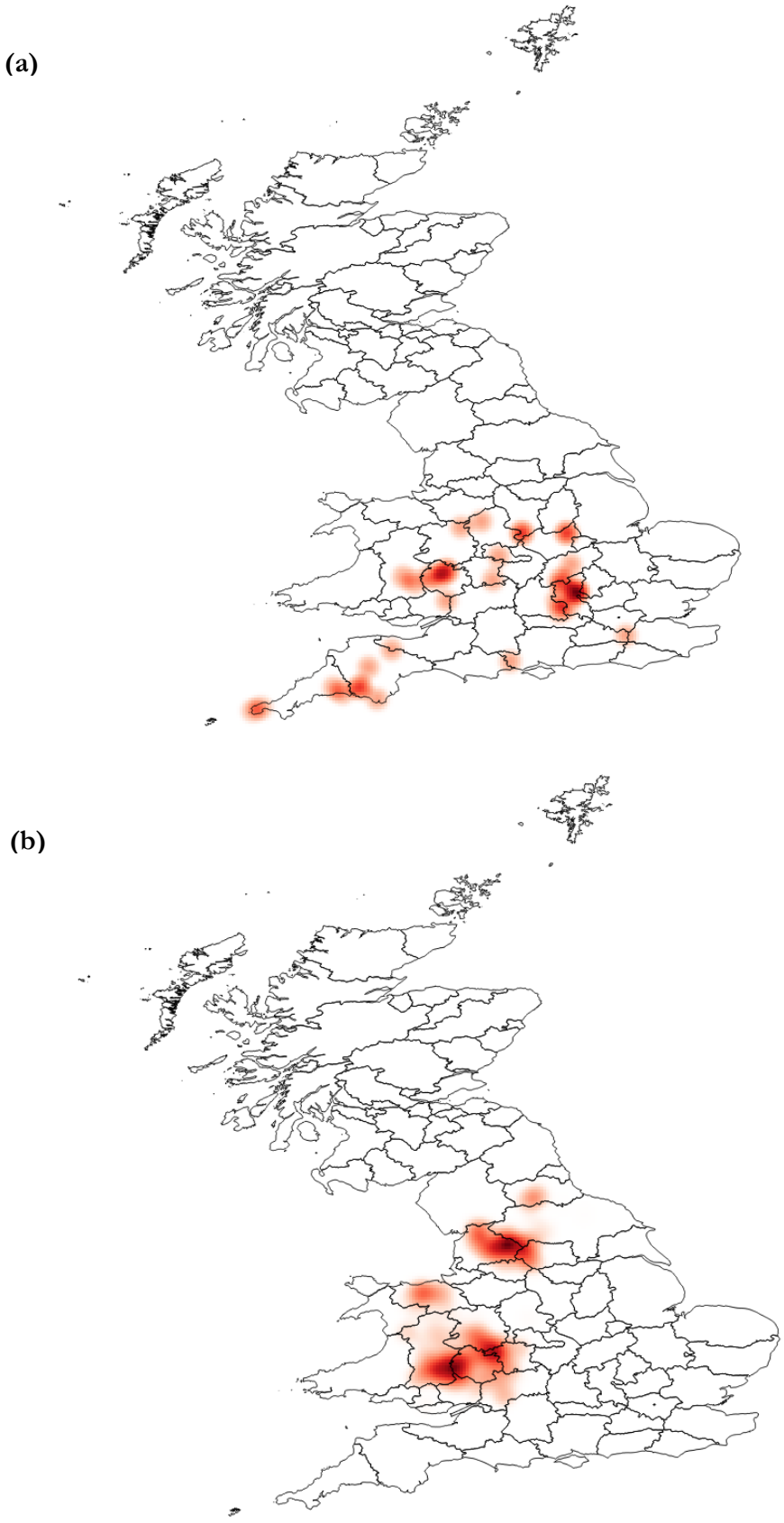
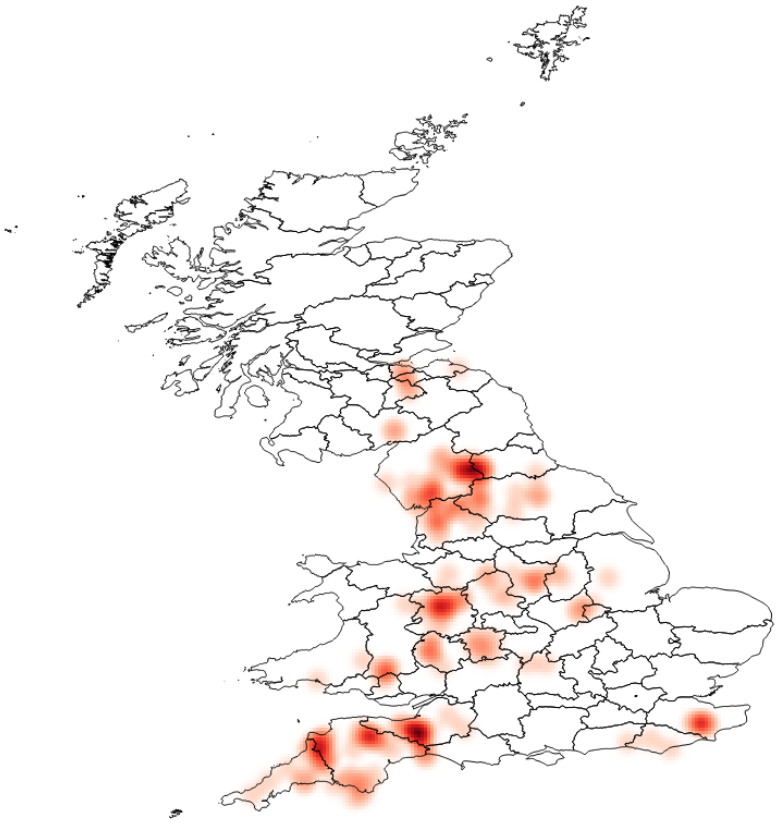


Fig. 3.23 (a) Reported cases of sheep scab in Great Britain in 1980 (b) Incidence of sheep scab in 1980 in the 1973 reintroduction simulation. The darker the shade of red, the higher the density of infected farms.

(a)



(b)

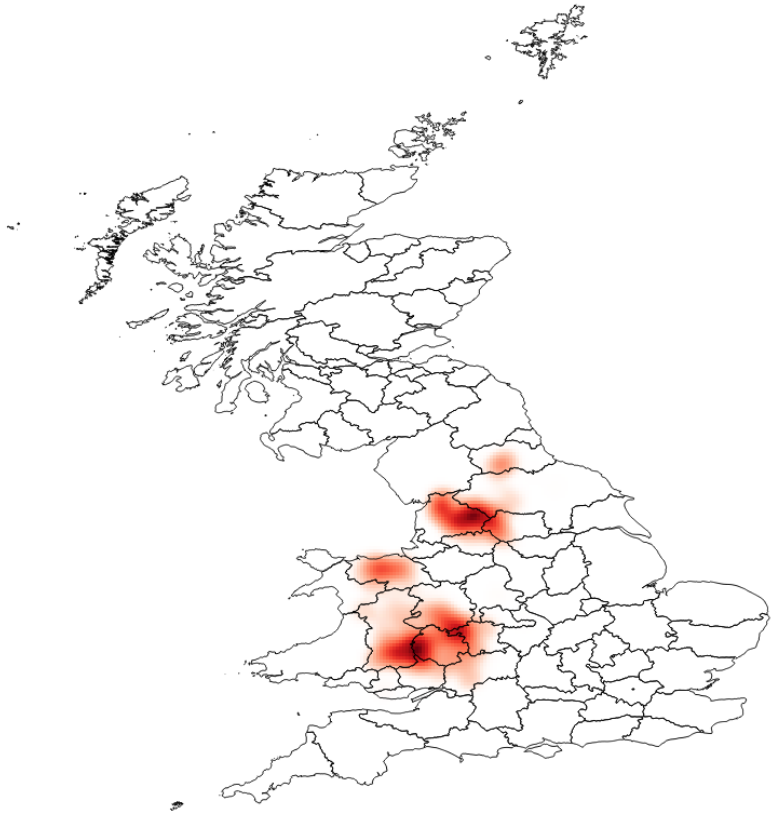


Fig. 3.24(a) Reported cases of sheep scab in Great Britain in 1984 (b) Incidence of sheep scab in 1984 in the 1973 Reintroduction Simulation. The darker the shade of red, the higher the density of infected farms.

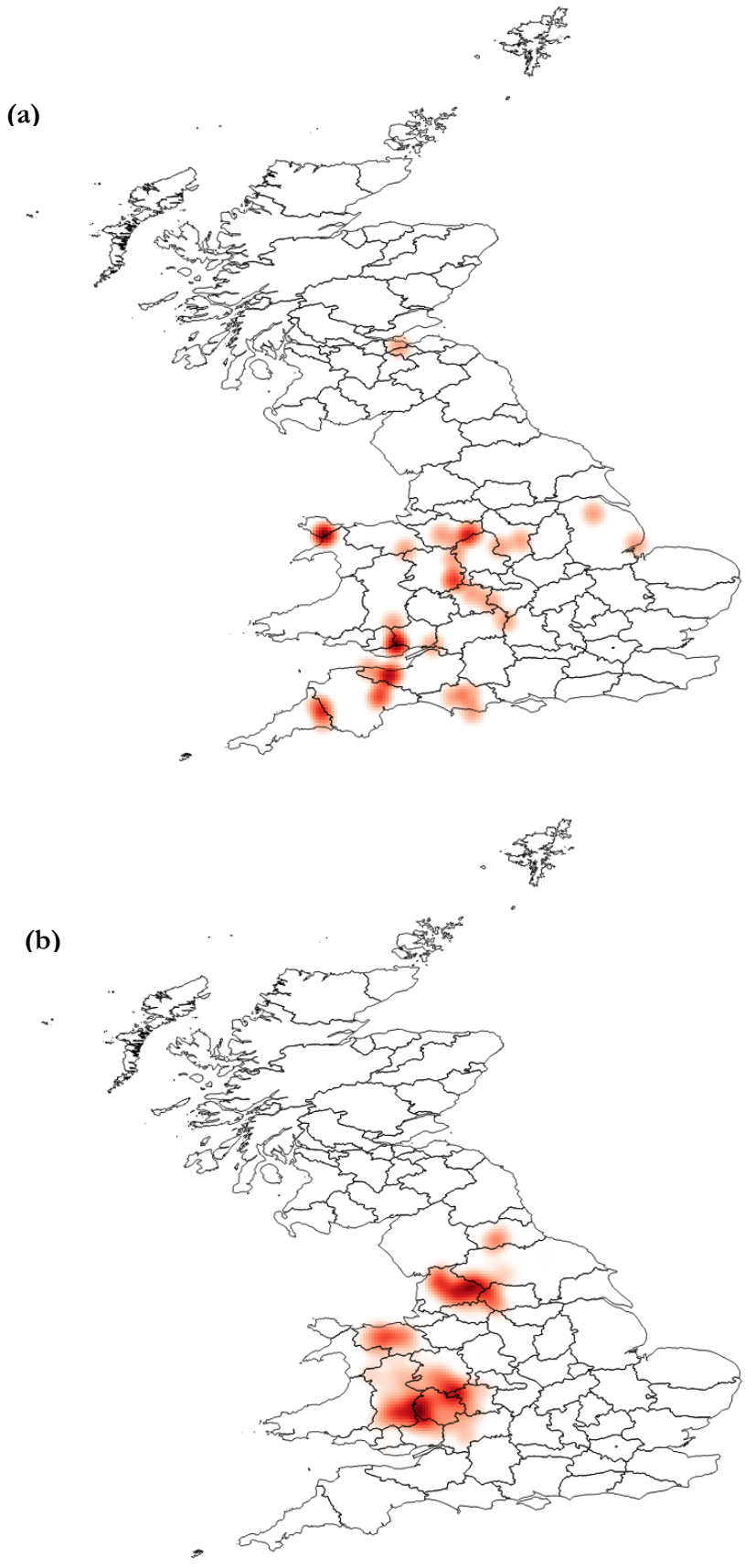


Fig. 3.25 (a)Reported cases of sheep scab in Great Britain in 1988 (b) Incidence of sheep scab in 1988 in the reintroduction simulation. The darker the shade of red, the higher the density of infected farms.

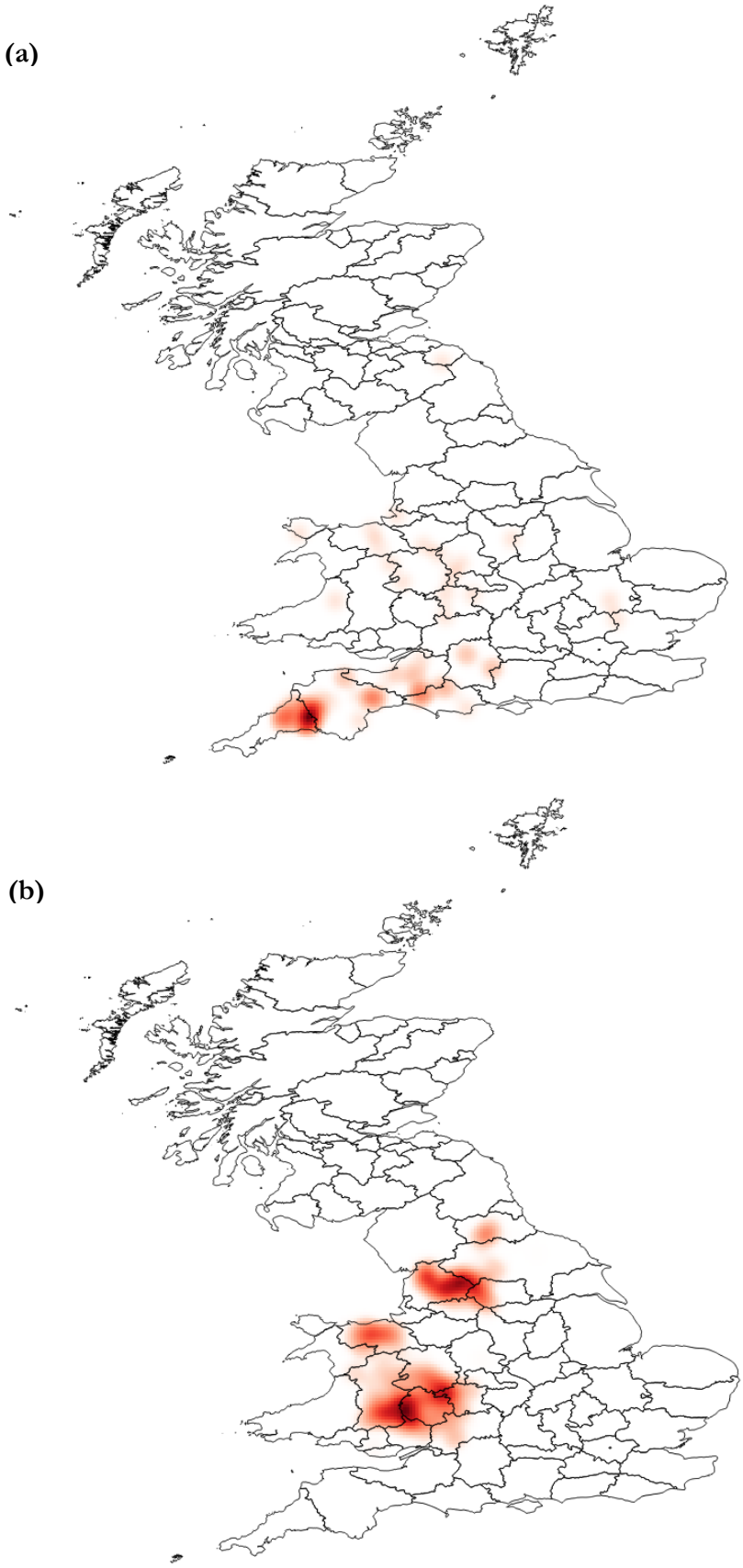


Fig. 3.26 (a) Reported cases of sheep scab in Great Britain in 1989 (b) Incidence of sheep scab in 1989 in the 1973 reintroduction simulation. The darker the shade of red, the higher the density of infected farms.

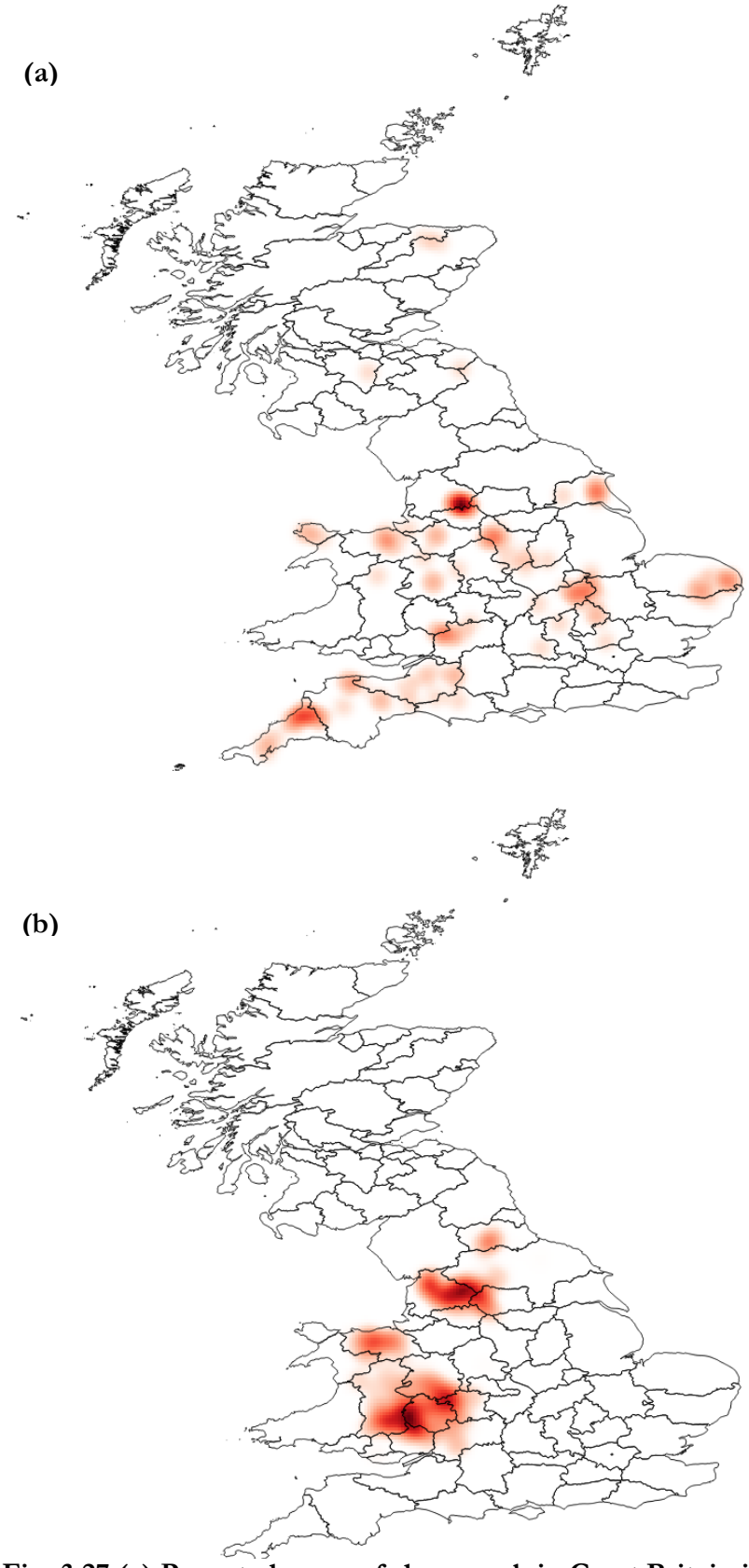


Fig. 3.27 (a) Reported cases of sheep scab in Great Britain in 1990 (b) Incidence of sheep scab in 1990 in the 1973 reintroduction simulation. The darker the shade of red, the higher the density of infected farms.

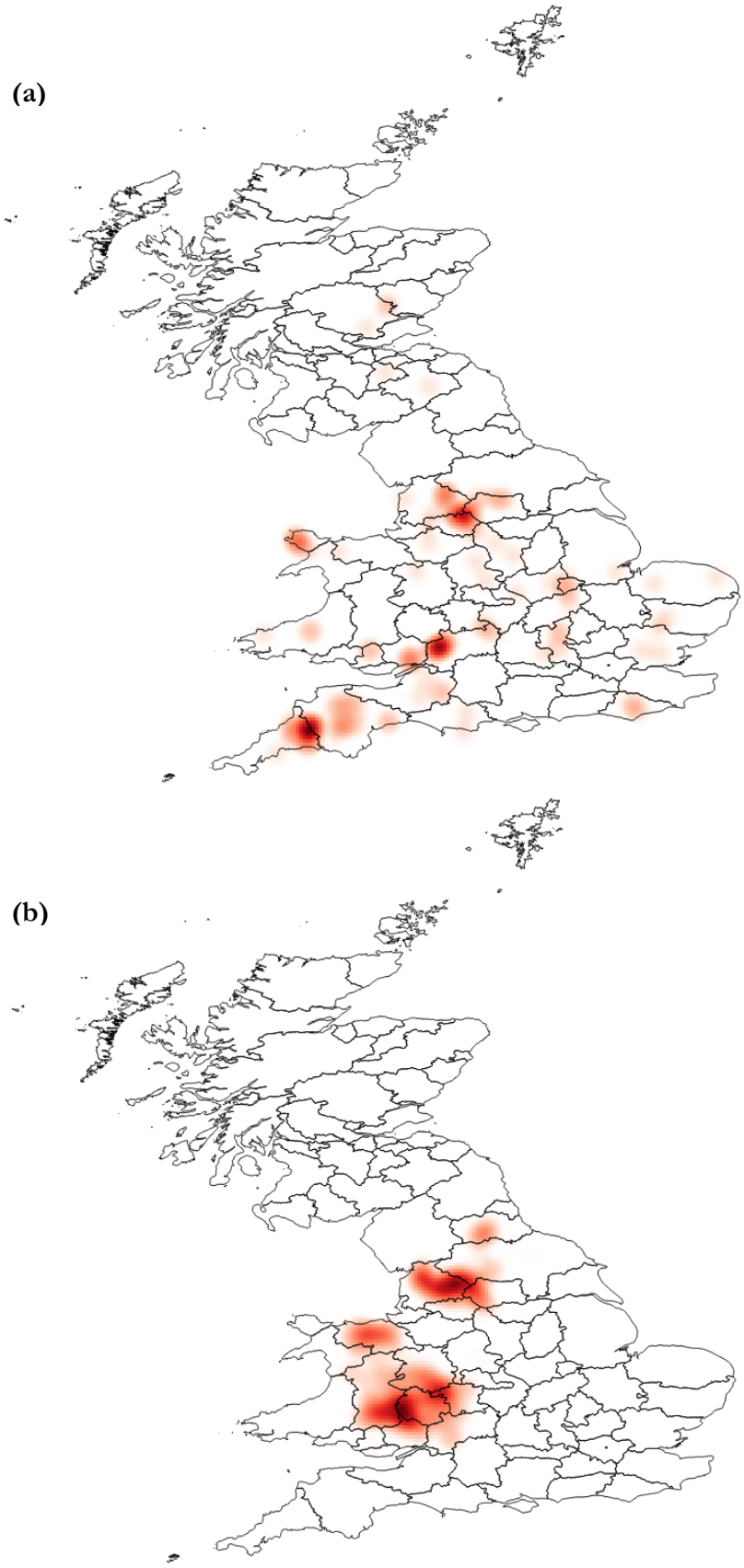


Fig. 3.28 (a) Reported cases of sheep scab in Great Britain in 1991 (b) Incidence of sheep scab in 1991 in the 1973 reintroduction simulation. The darker the shade of red, the higher the density of infected farms.

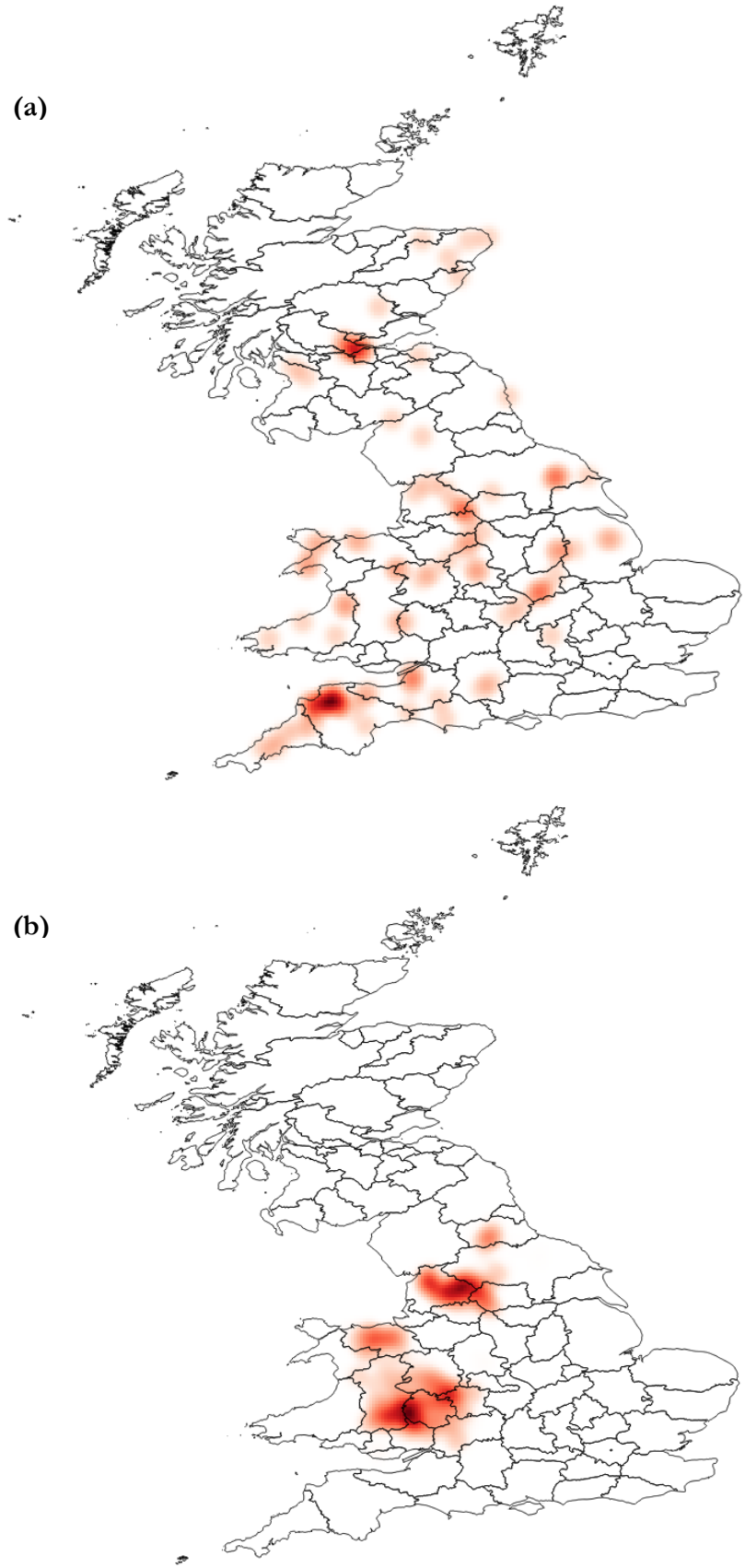


Fig. 3.29 (a) Reported cases of sheep scab in Great Britain in 1992 (b) Incidence of sheep scab in 1992 in the 1973 reintroduction simulation. The darker the shade of red, the higher the density of infected farms.

3.4.4 Results from the South West Simulation

As noted in 3.3.4.2, the model was also run again under the same conditions as the 1973 reintroduction simulation, but with the 19 initial farms infected in a different location, to allow for comparison. The South West of England was selected because this area had a similar proportion of common grazing farms (Fig. 3.13).

As with the 1973 reintroduction simulation, the number of infected farms in the South West simulation saw an initial sharp increase in prevalence, followed by a fairly constant prevalence (Fig. 3.30). Looking at the spatial results for the South West simulation (Fig. 3.31), it seems that, in the same manner as the 1973 reintroduction simulation, this result can be explained by the spatial dynamics. The area into which the disease was initially introduced in both simulations had a high density of sheep farms, with high connectivity (Fig. 3.11 and Fig. 3.12), a high R_0 (Fig. 3.14) and use of common grazing practices (Fig. 3.13). In both cases, the limiting factor to prevalence increase seemed to be the fact that disease had spread to the edges of the farm network. These results, when taken together, could signify that the spatial structure of farms does not allow for scab to spread across the whole of Great Britain by neighbour-to-neighbour contact only and that other means of transmission between farms are also important. Although the disease was introduced into only two areas in this chapter, future work could introduce scab to different areas in Great Britain to see if these results are replicated and whether a different pattern is seen when scab is introduced into areas where there is a low density of sheep farms.

Other studies have found that the spatial dynamics of sheep scab are important. It has been found that reported sheep scab outbreaks close in space were also significantly close in time according to space-time clustering. This was also true of the reverse (outbreaks close in time were close in space) (French et al., 1999). Elevation, precipitation and temperature have also been found to be significant predictors for the presence of sheep scab in England and could help to explain the higher prevalence of scab found in Wales, Scotland, South West England and Northern England (Rose, 2011). Scotland did not have many farms with a high degree of connectivity to other farms in the model described here (Fig. 3.11, Fig. 3.12) and so when initially infecting the model in Scotland, we may not expect to see a wide spread. This contrasts with survey data which suggests it is a region where the

prevalence of scab is the highest (Bisdorff et al., 2006; Rose, 2011). Therefore, perhaps it is the environmental variables that ensure that sheep scab is so persistent in Scotland, rather than the networks of sheep farms. Alternatively, although the distance between farms is wide, due to grazing practices, sheep from farms far apart from each other may still come into contact, allowing scab to be transmitted. Future versions of the model could take this into account if more data becomes available on grazing practices in Scotland.

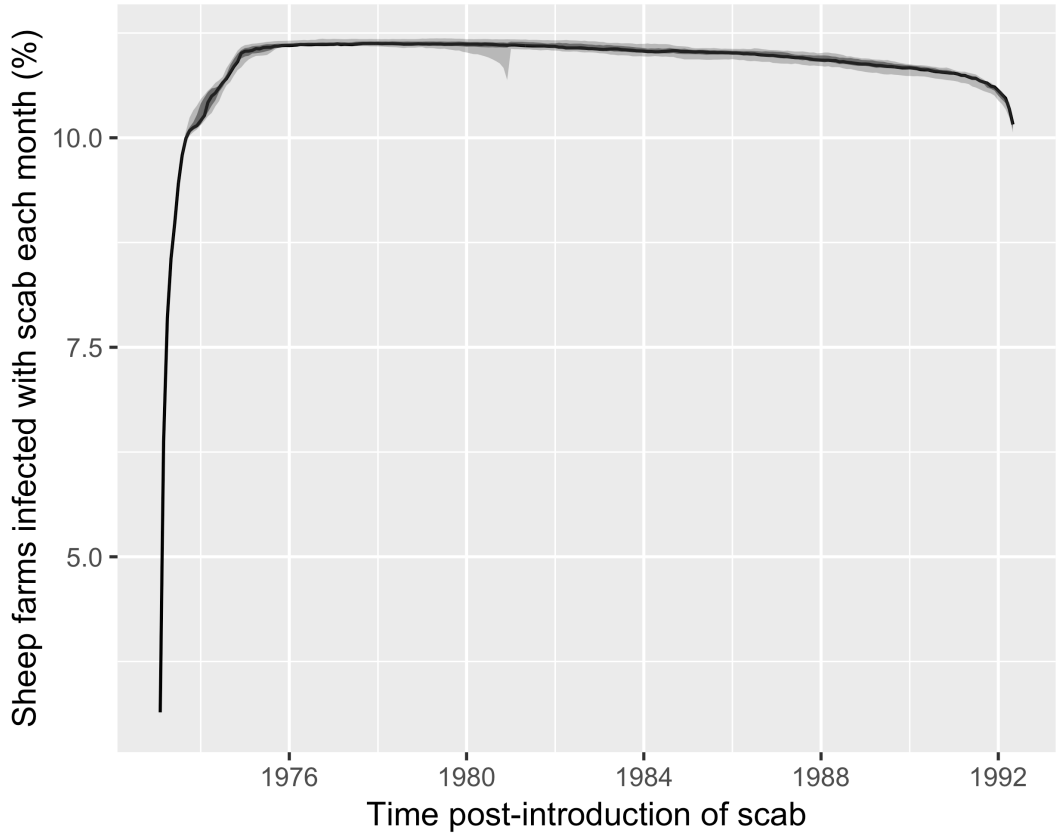
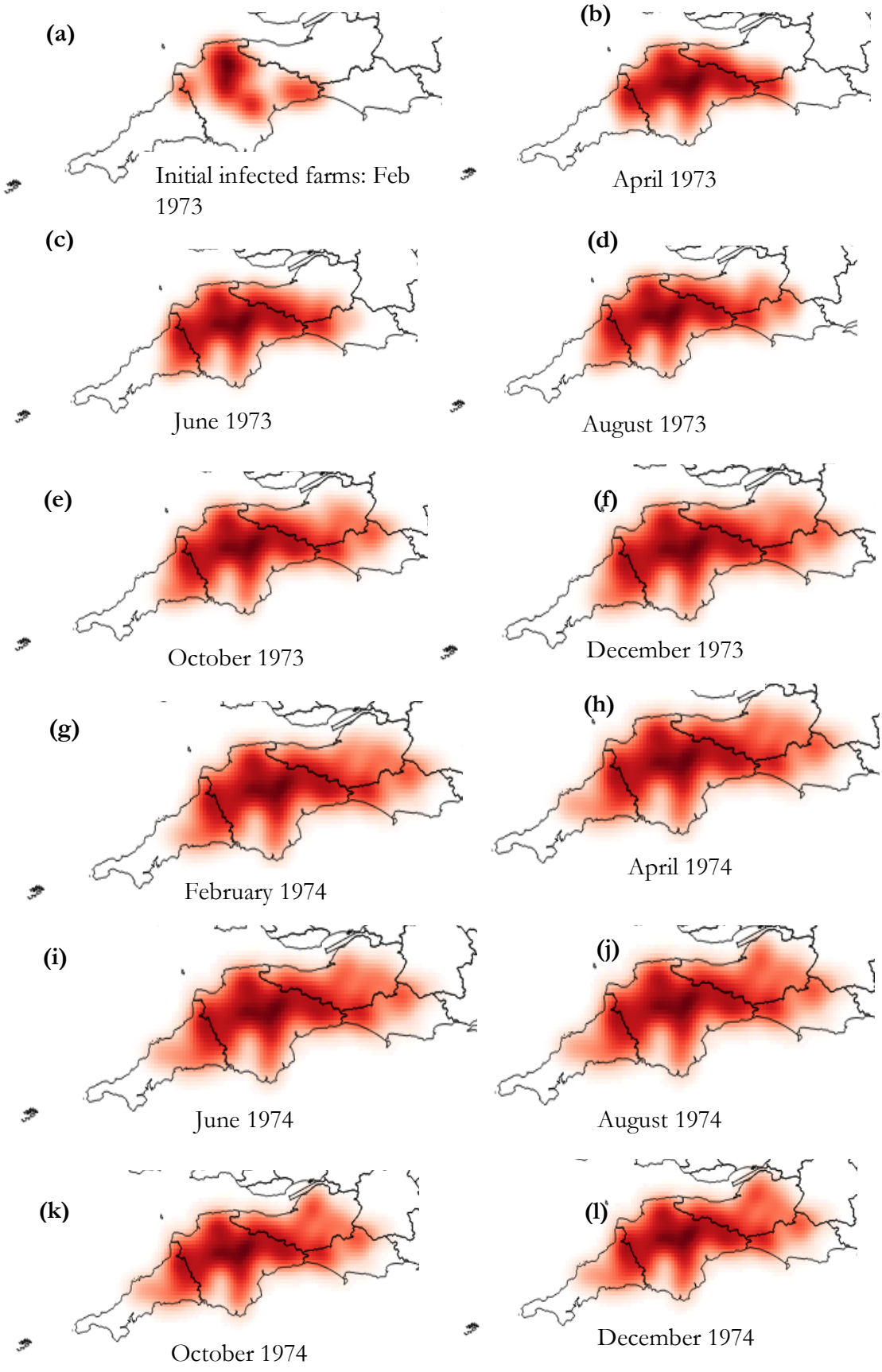


Fig. 3.30 The percentage of farms infested with sheep scab in Great Britain over time following the simulated reintroduction of sheep scab into 19 farms in the South West of England in January 1973 in a between-farm transmission model of sheep scab. The median result (black line), the interquartile range (dark grey shading) and the 2.5-97.5 percentiles (light grey shading) are given for repeated stochastic simulation runs (n=10). The total number of sheep farms is 68,620.


(a)
Initial infected farms: Feb 1973
(b)
April 1973
(c)
June 1973
(d)
August 1973
(e)
October 1973
(f)
December 1973
(g)
February 1974
(h)
April 1974
(i)
June 1974
(j)
August 1974
(k)
October 1974
(l)
December 1974

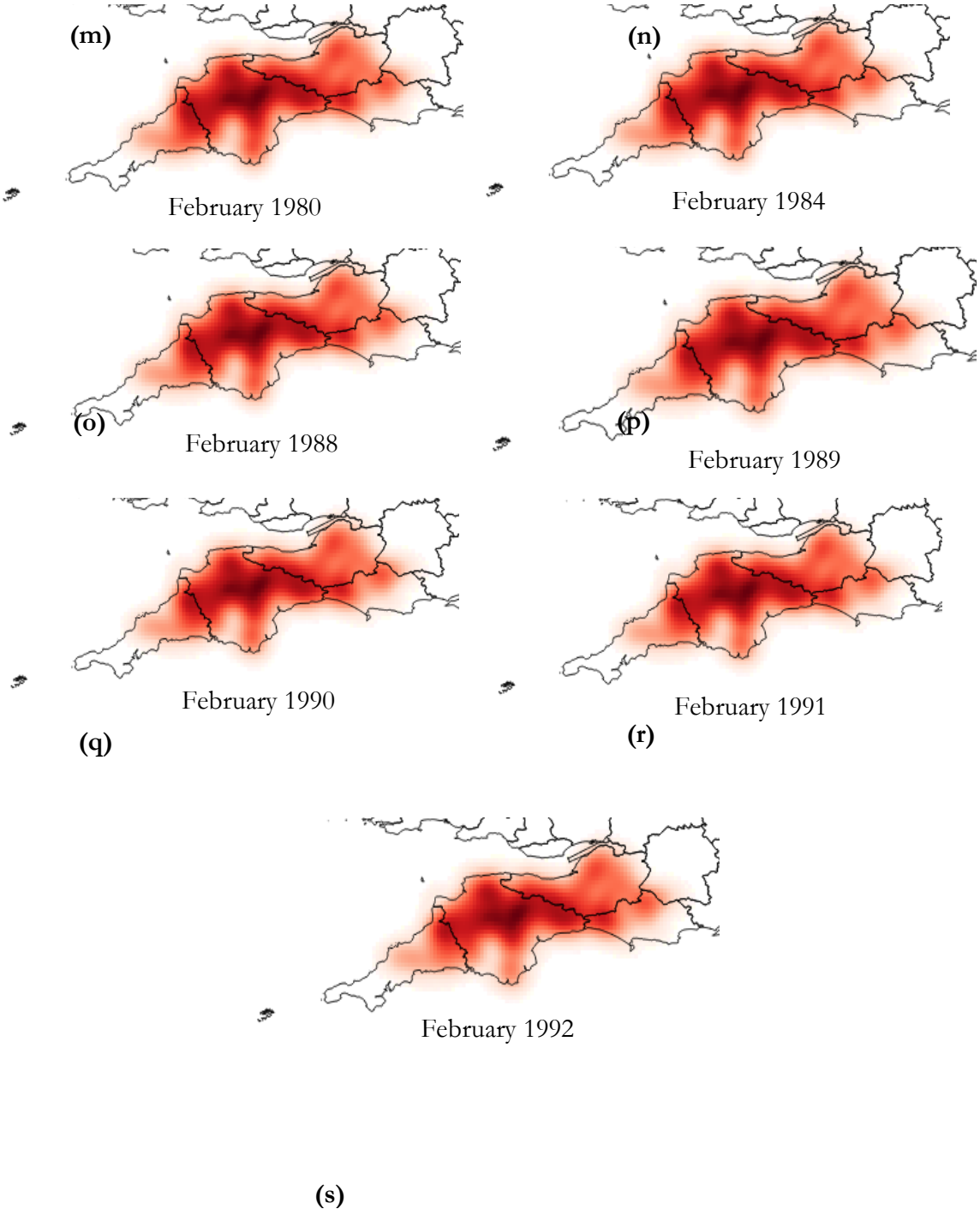


Fig. 3.31 (a-l) Monthly densities of sheep-scab- infected farms in 1973 and 1974 (m-s) Monthly densities of sheep-scab- infected farms in February of significant years (according to Fig. 3.30). These results are from one randomly-selected run of a simulation of the 1973 reintroduction of sheep scab in Great Britain where 19 farms in South-West England are initially infected. The darker the shade of red, the higher the density of infected farms.

3.4.5 Wider discussion

3.4.5.1 Model limitations

The model described in this chapter may have some limitations that have impacted the accuracy of the results. As with all models, it has been built on a number of assumptions and is limited by the data available. The network is built on the assumption that sheep scab can transmit between farms that are within a 2km radius of each other. This was based on the average size of a farm; however, sheep farms do greatly vary in size and so there are likely to be farms in the model that should be connected but are not and vice versa. Given the number of farms included, it was hoped that such variation in farm size would be subsumed within the model. Furthermore, as the area of each individual farm was not available, it was not possible to achieve greater accuracy in this. Another disadvantage of not having the area of each individual farm was that, as the model is density dependent, using the same transmission rate across all farms regardless of their size may see a higher spread than expected. This is addressed in the alternative metapopulation model in Chapter 5.

The mixing rate between farms was estimated from data and could be improved if more relevant data became available. In future, the range (41.10-70.73%), rather than the average of the core range of a flock (where sheep were found 50% of the time and where most activity occurs) that was shared with at least one other flock could be used to determine variable mixing rates for common grazing farms, rather than having one precise value across all common grazing farms. It was assumed that the mixing rate between islands was 1, but this may be an overestimate. The Scottish islands are separate units and are not the focus of the model described here, however, future studies that were interested in the epidemiology of sheep scab on a Scottish island may choose a different mixing rate for the island of interest.

Although nodes which were in water bodies were removed, there still may be farms that are connected in the model but would not be in reality due to water bodies or other physical obstacles between them. This was difficult to avoid without further complicating the model and the technique for selecting neighbouring farms, but perhaps could be included when looking at the spatial dynamics of sheep scab on a

smaller scale in future. In addition, perhaps assuming that all farms using the same common grazing area were connected might give more accurate results, as in the current version of the model, only farms which are physically close to each other and which used common grazing were able to transmit scab between them.

The parameter values used in the model were taken from Chapter 2, however, when compared to experimental data (Berriatua et al., 1999) the model output from Chapter 2 was found to not be from the same distribution. This is most likely to be due to the fact that the model conditions did not match the experimental conditions (see Chapter 4). Even if they did match, the experimental conditions from the Berriatua study are not representative of the majority of farms in Great Britain, with only 6 to 10 sheep used in each experiment, while the average flock size is 248 (Table 3.3). Therefore, although the models presented in Chapter 2 and in the current chapter do give some insight into the transmission dynamics of scab within and between farms in Great Britain, further work has been done in Chapters 4 and 5 in order to improve the accuracy of the model parameter values and the model structure.

3.4.5.2 Data limitations

The MAFF data on the reported outbreaks from 1973 to 1992 is self-reported and therefore is likely to be an underestimate of the number of scab cases seen at the time, even though it was a notifiable disease across the whole of Great Britain during these years (ADAS, 2008). Scab is often mistaken for blowfly strike (*Lucilia spp.*), chewing lice (*Bovicola ovis*) or scrapie and is hard to detect when the cases are subclinical (Bates, 1997a). In addition, sheep using common grazing are often not observed by farmers for long stretches of time (Rebanks, 2015), so farmers are often unaware when their flock is infected. Even when farmers are aware that they have a scab outbreak, they may not have always complied with the notification rules. The MAFF data may also have a spatial bias, as there may be inaccuracies in the grid references provided (French et al., 1999). A temporal bias may also be present due to clearance operations in common grazing areas and to the surge in detection of cases during investigations of outbreaks (French et al., 1999).

3.4.5.3 Software limitations

The software (STEM) used to build the models described in this chapter had some advantages over using a programming language. Firstly, the inbuilt GUI allowed videos of the spread of infection to be produced. In addition, although it is possible to modify models in STEM at the source code level, they can also be adapted using a drop and drag mechanism (Ford et al., 2006) which would be useful if the model was to be used in future by policy-makers who had limited or no programming ability. In addition, as the model becomes more complicated, using STEM provides less opportunities for coding mistakes, as seen with other types of specialised simulation software when compared to general programming languages such as R (Kopec et al., 2010). Therefore, STEM was a suitable software for the work presented in this chapter.

Although the STEM community have monthly phone conferences and a developer's forum to help with any developing issues or bugs (Douglas et al., 2019), there are still some disadvantages in using this software. The user documentation is not always up to date which does not always make it easy to use. In addition, the more a model is expanded, the less well STEM performs. In order to run the Chapter 3 model for a simulated time of 20 years with ten different stochastic seeds, it could take at least a week of real time. The framework of the model output (with each farm in the model as a column) meant that the files produced are extremely large when there are large numbers of farms (populations), often around 15-20 GB in size, and then the data then had to be tidied in order to analyse. It was not possible to modify STEM in order to change how the data is output from the model (personal communication with the software editors). In addition, the ability to add interventions is complicated, with workarounds as described in the Appendix of this thesis needed. If different interventions were to be applied in different locations, further workarounds would be needed in order for this to work effectively and it would greatly increase the running time of the model. Although there were less issues when developing the within-farm STEM model, the more the model was expanded, the greater the issues became. This limits the future expansion of the model described in this chapter within STEM and therefore a different software is used in the alternative metapopulation model presented in Chapter 5.

3.4.5.4 The future of sheep scab disease control

Despite the limitations of the model mentioned, it has produced results which provide new insights into the future of sheep scab disease control. The network of farms could be used in future control methods to identify regions where sheep scab can be contained if there are no long-distance movements. Regional control programs have generally been focused within county or country borders, for example, the sheep scab eradication program in Dartmoor (Lewis & Newton, 2005), or the funding provided by the Welsh Government for fighting sheep scab in Wales (Mitchell & Carson, 2019), however, the work here suggests that there are regions with high connectivity between neighbouring farms that cross county and country borders. If these regions were quarantined and treatment was used for all infected farms within these regions, then scab would not be able to be transmitted from neighbouring regions due to a lack of connections. This could lead to eradication, or at least a lower prevalence, of scab in Great Britain.

However, a national control program such as this would also need to involve the cooperation of government, farmers and vets across regions. Since the reintroduction in 1973, previous legislative and voluntary efforts to control scab have not succeeded and this is thought to be partly due to a lack of cooperation on the farmer's part; leading to a call for research on the economics of sheep scab control and farmer behaviour (Rose & Wall, 2012) . Although the recommendations made in this chapter could help to plan more effective interventions in the future, these interventions would only be successful with cooperation of farmers. Therefore, it is important to investigate farmer behaviour and economic incentives in order to understand more about what would motivate cooperation in farmers when planning interventions.

Chapter 4

AN EXPANDED MODEL OF WITHIN-FARM TRANSMISSION OF SHEEP SCAB

SUMMARY

The within-farm model matched the general trend of the experimental data from Berriatua et al. (1999) as parameterised in Chapter 2, but it was found to not be from the same distribution. When the parameters from Chapter 2 were used in the between-farm model across Great Britain (Chapter 3), the incidence was higher than expected from the data used for comparison (French et al., 1999). Therefore, the current Chapter aims to further investigate the parameterisation and structure of the within-farm model. An extra infectious compartment for carriers of scab is added to the model. The model is run stochastically and deterministically with two parameter sets: Parameter Set 1, which matches the conditions in the experimental data (Berriatua et al., 1999) and Parameter Set 2, which estimates parameters for conditions which take place over a longer time period than the experimental data.

The model outputs are confirmed to be from the same distribution as seen in experimental data by Berriatua et al. (1999) when using Parameter Set 1. However, when parameters are added to incorporate mortality, restocking and births and deaths (Parameter Set 2) and when a larger flock size is used than seen in the experimental data, the model output overestimates the experimental data. However, a similar endemic equilibrium is reached in all simulations run here. This could suggest that including these extra parameters is not important to the model output when investigating longer term dynamics. This was supported by the sensitivity analysis which demonstrates that the extra parameters used in Parameter Set 2 are not sensitive to the model output after running a simulation for ten years. Therefore, in future versions of the model, it is not necessary to include these parameters. However, in the initial stages of the outbreak, the time to the epidemic peak and endemic equilibrium may be quite variable between farms of different flock sizes and so this must be taken into consideration when selecting parameters for the model. The work presented here is used in Chapter 5 to build an alternative to the Chapter 3 metapopulation model.

4.1 INTRODUCTION: THE RATIONALE FOR THE ADAPTATIONS TO THE CHAPTER 2 MODEL

The within-farm model for sheep scab described in Chapter 2 did not produce an output that matches the distribution of the experimental data used to estimate the transmission rate (Berriatua et al., 1999). One reason that could explain the difference between the model output and the experimental data is the fact that all sheep were assumed to be equally infectious for the entire time period that they carried any *P.ovis* mites, which is thought to be up to two years (O'Brien, 1995), or at least two years (Babcock & Black, 1933). However, in the Berriatua study, all transmission occurred in the first eleven weeks of all trials, when mite numbers were at or close to their peak. Therefore, this chapter adds a "carrier" compartment to the model, where sheep are assumed to be infectious at a lower rate once mite numbers are past their peak.

The model parameters in Chapter 2 did not reflect all the conditions in the Berriatua study because it took place over a fourteen- week period and so other data from the literature was used, with longer-term dynamics in mind, to estimate the some of the parameters. However, this may have led to the differences seen between the model output and the Berriatua data. Therefore, here it was decided to use two parameter sets: one that matches the conditions in the Berriatua experiment (Parameter Set 1) and one that matches conditions that might be seen in the longer-term, including the addition of new parameters for natural births and deaths (Parameter Set 2), which might be important parameters in long term dynamics (Keeling & Rohani, 2008).

Two modelling software were used to build the model in Chapter 2. The deterministic model was built using R, an open-source programming language (R Core Team, 2019), while the stochastic model was built using the Spatial Temporal Epidemiological Modeler (STEM) which is a free open source software project run on *Equinox* (Eclipse) and coded in *Java* (Ford et al., 2006; Douglas et al., 2019). Although the results from the R deterministic model and the STEM stochastic model were consistent, in the current chapter, R was used to build both the deterministic and stochastic models to allow for a more accurate comparison.

The Uncertainty and Sensitivity analyses (UA and SA) were carried out here as described in Chapter 2. However, an alternative to the Partial Rank Correlation Coefficient (PRCC) was used for the sensitivity analysis of the recovery rate γ, since it appeared to have a non-monotonic relationship with the model output. As recommended by Marino et al. (2008), a test for common locations, the Kruskal-Wallis rank sum test, was used in the sensitivity analysis for γ.

4.2 AIMS

The work presented in this chapter aims to investigate why the Chapter 2 model output may have not been from the same distribution as the experimental data from Berriatua et al. (1999). It also aims to investigate how parameter values might be adapted to allow for longer term dynamics than were given in the experimental data.

4.3 METHODS

4.3.1 Software

R was used to develop and run the models described here. In R, the deterministic model was written using base R and the model equations were solved using the lsoda() function from the deSolve package (Soetaert et al., 2010). The stochastic model was written using base R and run using the GillespieSSA package (Pineda-Krch & Cannoodt, 2019) using the direct method as described by Gillespie (1977). R was also used to analyse and present the model output, often using the tidyverse (Wickham et al., 2019) and ggplot2 (Wickham, 2016) packages.

4.3.2 Model parameters, flowchart and equations

The within-farm sheep scab transmission model in Chapter 2 is based on the SIR (susceptible- infected- susceptible) compartmental model which is used widely in epidemiology (Kermack & McKendrick, 1927), but adapted for sheep scab.
The model structure from Chapter 2 has been adapted here so that there are two compartments for infected sheep (Fig. 4.1). Sheep in the "infected" compartment are now defined as those in the early to medium stages of infection where *P.ovis* mite numbers increase to a peak then decline to a low number of mites. There is an addition of a "carrier" compartment which is for sheep that have gone past the peak of infection but are still carrying *P.ovis* mites. It is assumed that only infected sheep (not carriers) will die from having scab, as the majority of the time period that sheep are carriers they exhibit limited or no clinical symptoms (Bates, 2007) and causes of death by scab are all related to side effects of severe hypersensitivity responses such as secondary bacterial infections, condition loss, hyperthermia (Bates, 2007) or stimulation which leads to epileptiform convulsions (Bygrave et al., 1993).
The model parameters are described in Table 4.1 and match those given in Chapter 2, where applicable (Table 2.1), unless otherwise specified.

Natural births and deaths are included in the model version described here on the assumption that there is a natural host "lifespan" and that the population size does not change over time (Keeling & Rohani, 2008).

As in Chapter 2, a recovered compartment is not included, since it is thought that sheep do not usually "recover" without treatment even if they appear to have no clinical signs. They will usually still be a carrier of the mite for periods of up to two years and are still able to spread the mites which cause the disease to other individuals (Babcock & Black, 1933; O'Brien, 1995). Therefore, a transition is included whereby infected individuals move back from the Carrier compartment to the susceptible compartment after two years (with recovery rate γ, Fig. 4.1.) (this transition was previously from the infected to the susceptible compartment).

The model is density dependent as described in Chapter 2 (2.3.2.1); however, the transmission term has been expanded to include the impact of carriers on transmission (equation 4.1).

Table 4.1. The symbols used to represent parameters in a within-farm SICTD (susceptible-infected-carrier-treated-dead) sheep scab model. When applicable, the symbols correspond to those in the parameter glossary in Keeling and Rohani (2008).

Symbol	Meaning
S, I, C, T, D	Absolute numbers of susceptible (S), infected (I), carrier (C), treated (T) individuals and dead (D) (from disease)
N	The total number of individuals in all disease states (not including D, which is not a true disease state)
μ	$\frac{1}{lifespan\ of\ average\ sheep}$
γ	Recovery rate from being highly infectious (in the infected state). $\frac{1}{\gamma}$ is the period of infection
m	Disease-induced mortality rate
p	Probability of dying from infection
q	The proportion of acute infected that become carriers. (1-q) recover without becoming carriers.
Γ	Rate at which individuals leave the carrier class
β	Transmission rate of infection
R_0	Basic reproductive ratio
R(∞)	Final epidemic size
ε	Reduced transmission rate from carriers compared to infectious individuals
Ψ	Protection rate
θ	Protection loss rate
α	Restocking rate (note this is the same as ξ in Chapter 2, but had to be changed here when using the GillespieSSA package)

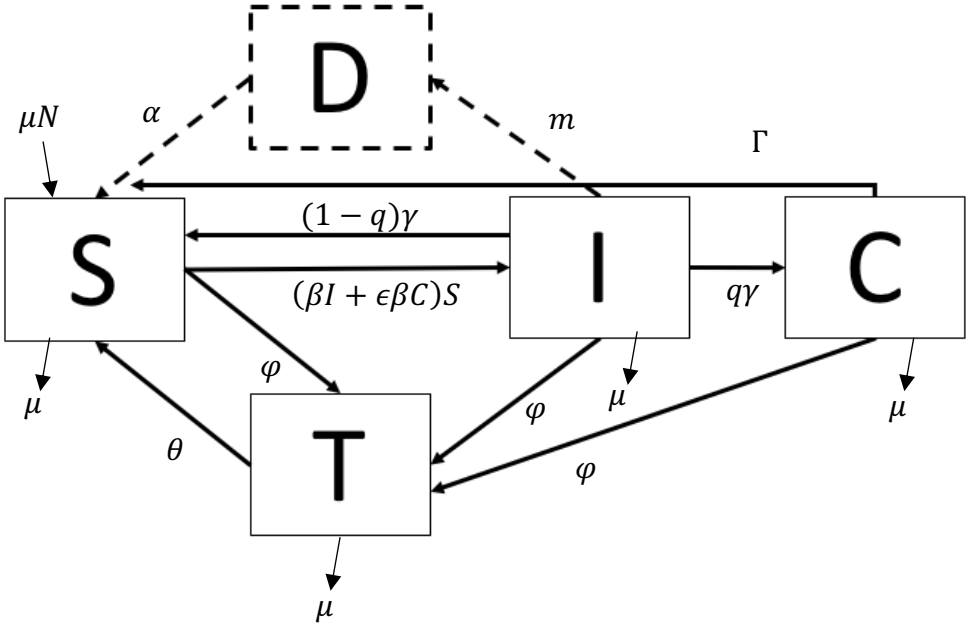


Fig. 4.1. Compartments and transitions in a SICTD model for sheep scab based on the SIR disease compartment model developed by Kermack & McKendrick (1927). "S" is a compartment for susceptible sheep in a farm, "I" is for sheep in the early to medium stages of infection, "C" is for sheep past the peak of infection but still carrying *P.ovis* mites, "T" is a compartment for treated sheep (those that have been treated for scab with a product that has residual activity) and "D" is for sheep that have died from scab. The D compartment is included for convenience so that the farm re-stocks to its original size, but is not a true compartment of the model (indicated by the dashed lines). It is assumed that the birth rate is equal to the natural death rate. The Greek symbols (defined in Table 4.1) represent the rates at which individuals enter and leave compartments and the arrows indicate the direction of movement.

4.3.3 The deterministic model

There are five compartments in the model: "S" is a compartment for susceptible sheep in a farm, "I" is for sheep in the early to medium stages of infection, "C" is for sheep past the peak of infection but still carrying *P.ovis* mites, "T" is a compartment for treated sheep (those that have been treated for scab with a product that has residual activity) and "D" is for sheep that have died from scab. The D compartment is included for convenience so that the farm re-stocks to its original size. It is assumed that the birth rate is equal to the natural death rate. Individual sheep on a farm move from one compartment to the other as described by the deterministic differential equations 4.1-4.5 describing the rate of change of the number of sheep in each disease state over (continuous) time:

$$\frac{dS}{dt} = \mu N - (\beta I + \epsilon\beta C)S + \gamma(1-q)I + \Gamma C + \alpha D + \theta T - \Psi S - \mu S \quad 4.1$$

$$\frac{dI}{dt} = (\beta I + \epsilon\beta C)S - \gamma I - mI - \Psi I - \mu I \quad 4.2$$

$$\frac{dC}{dt} = \gamma q I - \Gamma C - \Psi C - \mu C \quad 4.3$$

$$\frac{dD}{dt} = mI - \alpha D \quad 4.4$$

$$\frac{dT}{dt} = \Psi(I + C + S) - \theta T - \mu T \quad 4.5$$

$$N = S + I + C + T \quad 4.6$$

where the parameters given are described in Table 4.1. Equations 4.1-4.5 can be solved deterministically using solvers for ordinary differential equations (ODEs) and are solved here using the lsoda() function in R from the deSolve package (Soetaert et al., 2010). The count of the D compartment is not included in the total count (N), since the sheep in compartment D are not live sheep.

4.3.4 The stochastic model

The direct method from Gillespie (1977) was used to simulate the model stochastically (events given in Table 2.2) using the GillespieSSA package in R (Pineda-Krch & Cannoodt, 2019). The algorithm for the direct method has been written in pseudo code by Keeling and Rohani (2008) as given here:

1. Label all possible events $E_1, \ldots, E_n$.
2. For each event determine the rate at which it occurs, $R_1, \ldots, R_n$.
3. The rate at which any event occurs is $R_{total} = \sum_{m=1}^{n} R_m$
4. The time until the next event is $\delta t = \frac{-1}{R_{total}} \log(RAND_1)$.
5. Generate a new random number, $RAND_1$. Set $p = RAND_2 * R_{total}$.
6. Event p occurs if: $\sum_{m=1}^{p-1} R_m < P \leq \sum_{m=1}^{p} R_m$
7. The time is now updated, $t \rightarrow t + \delta t$, and event p is performed
8. Return to step 2.

The code for the stochastic model is provided in the Appendix and the state change matrix specifying the events in the stochastic model is given in Table 4.2.

Table 4.2 A state change matrix for a stochastic SICTD model of sheep scab. The matrix indicates the nature of the change (0 - no change, 1 - gaining individuals, -1 - losing individuals) in each disease state (rows) according to an event (columns). The propensity vector gives the corresponding event functions describing the probabilities that events will occur over the next time interval *[t, t+dt]*. The definition of parameters and disease states are given in Table 4.1.

Event	Natural births	Natural deaths (Susceptible)	Natural deaths (Infected)	Natural deaths (Carrier)	Natural deaths (Treated)	Susceptible sheep becoming infected	Infected sheep recovering	Infected sheep becoming carriers	Carriers recovering	Disease mortality	Restocking	Treatment of sheep (Susceptible)	Treatment of sheep (Infected)	Treatment of sheep (Carrier)	End of protection conferred by treatment
Propensity vector	μN	μS	μI	μC	μT	$(\beta I + \epsilon\beta C)S$	$\gamma(1-q)I$	$\gamma q I$	ΓC	mI	αD	$\Psi(S)$	$\Psi(I)$	$\Psi(C)$	θT
S	1	-1	0	0	0	-1	1	0	1	0	1	-1	0	0	1
I	0	0	-1	0	0	1	-1	-1	0	-1	0	0	-1	0	0
C	0	0	0	-1	0	0	0	1	-1	0	0	0	0	-1	0
D	0	0	0	0	0	0	0	0	0	1	-1	0	0	0	0
T	0	0	0	0	-1	0	0	0	0	0	0	1	1	1	-1

4.3.5 Parameter estimation

The model parameters are first estimated using conditions and results from a prospective study (Parameter Set 1) where a sheep infected with scab was introduced into a naïve flock (Berriatua et al., 1999, fully described in Chapter 2). However, as this study only took place over a period of 100 days, a second set of parameter values were estimated using alternative data sources which take into account longer term dynamics (Parameter Set 2). The values used in each parameter set are justified for each parameter described in this section and are summarised in Table 4.3. All parameters here are calculated as rates per day (days^{-1}). Uncertainty analysis and sensitivity analysis is carried out for all parameters (sections 4.3.6.3, 4.4.3).

4.3.5.1 Recovery rate (γ)

The recovery rate γ can be shown (mathematically) to be:

$$\gamma = \frac{1}{average\ infectious\ period} \qquad 4.6$$

assuming a constant recovery rate or an exponentially-distributed infectious period. Here, this represents the rate at which individuals recover from being highly infectious with scab (in the "I" compartment). Across the five Berritauta experiments, all transmissions occurred within the first eleven weeks (77 days) of the experiment (Berriatua et al., 1999). In addition, the peak number of mites on index cases were seen on week 11 on average (Fig. 4.2), when plotting the number of mites on index cases over time, from when lesions were first established on the index case (prior to the experiment) to the end of the experiment (these data were only available for index cases 2A, 2B and 2C). Therefore, 11 weeks is assumed to be the average period of infection for the acute phase. After this point, the index cases of infected sheep either recovered from scab and became susceptible again or had a lower population size of *P.ovis* mites and were less infectious and considered to be "Carriers" (Fig. 4.2 and Fig.1 from Berriatua et al. 1999). Therefore, the rate at which individuals recover from being highly infected in the model is assumed to be:

$$\gamma = \frac{1}{77}\ \text{days}^{-1}$$

This value is used in both parameter sets.

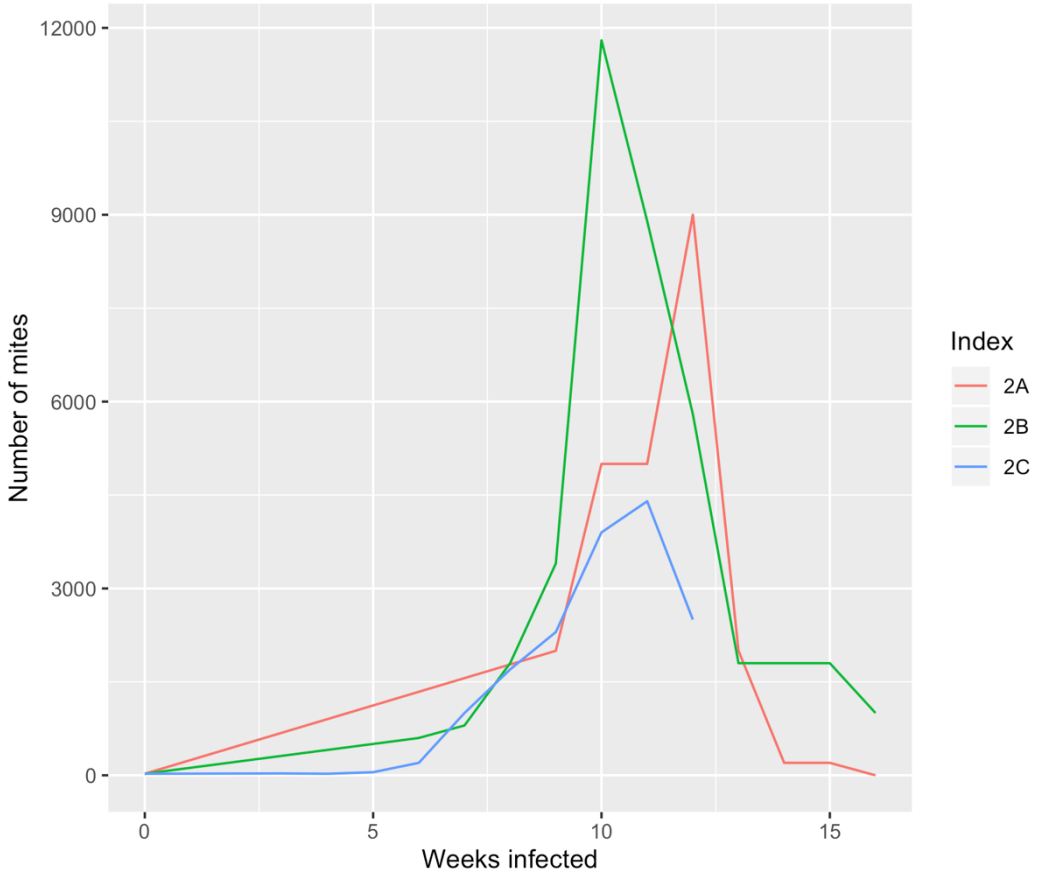


Figure 4.2 The number of mites on index cases of scab over time in experiments by Berriatua et al. (1999). The number of mites on day 0 were given in Table 1 of Berriatua et al. (1999). The number of mites on each index case during the experiment is taken from Fig. 1 of Berriatua et al. (1999). The number of weeks infected shown is the number of weeks for which lesions had been established prior to introduction to the naïve flock (assumed to be the period of infection of the index prior to the experiment), added to the number of weeks since the index case was introduced to the naïve flock. Data on both these time periods was only available for Index cases 2A, 2B and 2C, although there were three other index cases used in the Berriatua study.

4.3.5.2 *The proportion of acute infections that become carriers (q)*

The acute infectious cases that recover at rate γ either become carriers of scab, or susceptible. In the model, γ is scaled by the proportion of acute infections that become carriers (*q*).

At the end of the Berriatua study, two out of four index cases still had mites at the end of the study (the index case from Trial 1 is not included since it was removed four weeks into the study). This is used to calculate the proportion of acute infections (in disease state "I") that become carriers of scab (disease state "C"). Therefore:

$$q = \frac{2}{4}$$

Those that recover without becoming carriers *(1-q)* recover from scab and become instantly susceptible. This is reflective of the other two out of four index cases which had no mites at the end of the study. This value is used in both parameter sets.

4.3.5.3 *Recovery rate for carriers (τ)*

It has been suggested that the period of infection (including both the acute infectious stage and the carrier stage) for sheep scab without treatment may be two years (O'Brien, 1995), or at least two years (Babcock & Black, 1933). Although clinical signs might not be present on an infected individual for the whole two year period, mites can remain concealed within cryptic sites on a sheep, such as hidden skin folds or the ear (Babcock & Black, 1933; Bates, 1997a) and even with only one pregnant female mite present, if passed to another host, will establish an infection on that host (van den Broek & Huntley, 2003b).

As discussed in section 4.3.5.1, the period of infection for the acute phase is thought to be approximately eleven weeks. Therefore, it is assumed that the period of infection for the carrier phase is the total period of infection (two years and assuming neither are leap years), minus eleven weeks. Therefore, the rate at which carriers recover and become susceptible is assumed to be (for both parameter sets):

$$\tau = \frac{1}{653}\ \text{days}^{-1}$$

4.3.5.4 *Natural births and deaths (μ)*

In the Berriatua study, no natural births or deaths occurred (Berriatua et al., 1999) and therefore, when fitting to the Berriatua data (Parameter Set 1), it is assumed the natural birth and death rate is:

$$\mu = 0$$

The Berriatua study took place over a period of fourteen weeks; a time period where it is unlikely that many sheep would be born or die naturally. However, when investigating longer term dynamics, it might be important to include natural births and deaths. The natural life expectancy of a sheep, where slaughter or disease does not occur, is approximately twelve years (Rando & Chang, 2012). Therefore, in the version of the model which uses parameters for longer term dynamics (Parameter Set 2):

$$\mu = \frac{1}{4380}$$

4.3.5.5 *Disease -induced mortality rate (m)*

In the Berriatua study, there were no deaths as a result of scab (Berriatua et al., 1999). Therefore, in Parameter Set 1, which matches the conditions of the experimental data, the disease-induced mortality rate is:

$$m = 0$$

However, in the Berriatua study, sheep that were displaying severe symptoms of scab that could have led to mortality were removed and replaced with alternative infected index cases. This was due to animal welfare concerns. These severely infected sheep may have died without intervention. In addition, if the experiments had continued past fourteen weeks, then more sheep may have died from contracting scab. Therefore, in Parameter Set 2, disease mortality is calculated using:

$$m = \frac{\rho}{1-\rho}(\gamma + \mu) \qquad 4.7.$$

where ρ is the probability that an infected individual dies from infection before either recovering or dying from natural causes, γ is the recovery rate and μ is the natural per capita death rate (Keeling & Rohani, 2008). This is the same as equation 2.7.

As in Chapter 2 (described in section 2.3.3.2), the value of *p* is estimated to be $\frac{1}{3}$. Using the values for γ and μ in Parameter Set 2, the disease mortality for this parameter set is estimated to be:

$$m = \frac{\frac{1}{3}}{1-\frac{1}{3}}\left(\frac{1}{77}+\frac{1}{4380}\right)$$

$$m = \frac{1}{151}$$

4.3.5.6 Reduced transmission of scab by carriers (ε)

When individuals are considered to be carriers of scab, the mite population they harbour is past its peak size and therefore carriers are less likely to transmit mites to other individuals (directly or via the environment) compared to acute infected sheep with higher numbers of mites. This is captured in the model by the use of a scaling factor (ε) for the transmission rate (β).

In the Berriatua study, all transmission occurred during the first eleven weeks of the experiments, which in the model, is considered to be when individuals are "Infected" and includes the period where the mite population reaches its peak. For the two index cases (2B and 2C) with mites at the end of the experiment, the number of mites they have at week 12 is about one third compared to the average number of mites they had in the previous eleven weeks (Fig. 2, Berriatua et al., 1999). Therefore, it is assumed here that the rate of transmission for carriers is approximately one third of the transmission rate for acute infected individuals:

$$\varepsilon = \frac{1}{3}$$

in both parameter sets.

4.3.5.7 Transmission rate (β) and R0

As mentioned in the introduction, sheep scab can be transmitted directly via sheep-to-sheep contact and indirectly via contact with mites in the environment. However, the transmission rate is estimated using data from a study where the mode of transmission was not determined (Berriatua et al., 1999). Therefore, determination between these two modes of transmission is not used in the model and so the transmission parameter includes the impact of both direct and indirect transmission.

The transmission rate, β, per individual can be calculated by rearranging the equation for R_0:

$$R_0 = \frac{\beta}{\gamma + m + \mu} + \frac{q\gamma}{(\gamma + m + \mu)} \cdot \frac{\varepsilon\beta}{(\tau + \mu + m)} \qquad 4.8.$$

Where R_0 is the "number of secondary infectives per index case in a naïve population of susceptibles" (Keeling & Rohani, 2008). The equation given is for infections with a carrier state and is adapted from the equation given in Keeling and Rohani (2008). All other parameter symbols match those already defined in Table 4.1. It is assumed that mortality can occur at any time point during infection.
This equation can be rearranged to make β the subject:

$$\beta = \frac{R_0(\gamma + \mu + m)(\Gamma + \mu + m)}{\Gamma + \mu + m + \mathcal{E}q\gamma} \qquad 4.9.$$

The values of these parameters (excluding β and R_0) have already been described in earlier subsections of 4.5.6. However, some of the values are different between the two parameter sets and so β is also estimated twice here, once for each parameter set. R_0 can be estimated using equation 4.10 and data from Berriatua et al. (1999).
In the Berriatua et al (1999) study, although in the abstract it states that 34 out of 40 scab-naïve sheep became infected following the introduction of an infected sheep which was the final size used in Chapter 2, upon deeper investigation of the full text this could not be replicated. In the experimental results 33 out of 39 cases were found to be infected at the end of the experimental period. This is used to recalculate the R_0 numerically using guidance and the following equation from Keeling and Rohani (2008):

$$1 - R(\infty) - S(0)e^{e^{-R(\infty)R_0}} = 0 \qquad 4.10.$$

Assuming that the entire population is susceptible, then S(0) = 1. The final proportion of recovered individuals, or the total proportion of the population that gets infected (so in this case $\frac{33}{39}$ or 0.85) is R(∞).

Substitute these values in and rearrange to get:

$$\frac{6}{39} = e^{-\frac{33}{39}R_0}$$

Log both sides of the equation to get:

$$\ln(\frac{6}{39}) = -\frac{33}{39}R_0$$

Rearrange:

$$\frac{\ln\frac{6}{39}}{-\frac{33}{39}} = R_0$$

$$R_0 = 2.212\ (3dp)$$

This value of R_0 looks very similar to the value obtained by looking visually at Fig 2.2.

Using equation 4.9 and when fitting the model to the Berriatua data (using Parameter Set 1):

$$\beta = 1.19 * 10^{-2}\ _{(3sf)}$$

and when using Parameter Set 2:

$$\beta = 3.48 * 10^{-2}\ _{(3sf)}$$

β is the risk of transmission from an infected sheep to a susceptible sheep per day (assuming homogenous mixing). In a flock of 100 sheep, where 1 is infected and 99 are susceptible, when using Parameter Set 1 there would be about 1 new sheep infected per day and 3.5 new sheep infected per day when using Parameter Set 2 (this is calculated using $\frac{1}{\beta \times S}$).

4.3.5.8 Protection rate (ψ) and protection loss rate (θ)

For the same reasons given in Chapter 2, the protection rate, ψ, and the protection loss rate, θ, are set to zero, as treatment was not included in the model simulations here. If the values for these parameters were greater than zero, carriers of scab are subject to the same protection transitions as susceptible and infected sheep.

4.3.5.9 Restocking rate (α)

No individuals died of scab in the Berriatua study and so the susceptible population of sheep were not restocked (although index individuals were replaced with alternative index cases in Trial 1). Therefore, when fitting the model to the Berriatua data the restocking rate:

$$\alpha = 0$$

However, when running the model over a longer time period, it is likely that restocking would occur and so the restocking rate has a default value of 1 (due to the assumption that the flock size is constant). This means that all individuals who die from infection and move to the "D" compartment are continuously replaced by susceptible individuals in the flock. This assumes that farmers will instantly replace any individuals lost to sheep scab. In other versions of the model, if a slower rate of replacement is required, then values between 0 and 1 can be used.

Table 4.3 Parameter values for two parameter sets used in a SICTD model for sheep scab. Parameter Set 1 was estimated to match the conditions in experiments by Berriatua et al. (1999), while Parameter Set 2 was estimated using other data from the literature which might be important for long term dynamics.

Parameter	**Parameter Set 1**	**Parameter Set 2**
Recovery rate for infecteds (γ)	$\frac{1}{77}$	$\frac{1}{77}$
Scaling rate for infecteds becoming carriers (q)	$\frac{2}{4}$	$\frac{2}{4}$
Recovery rate for carriers (τ)	$\frac{1}{653}$	$\frac{1}{653}$
Natural birth and death rate (μ)	0	$\frac{1}{4380}$
Disease mortality rate (m)	0	$\frac{1}{151}$
Scaling rate for transmission by carriers (ε)	$\frac{1}{3}$	$\frac{1}{3}$
Transmission rate (β)	$1.19 * 10^{-2}$	$3.48 * 10^{-2}$
Protection rate (ψ)	0	0
Protection loss rate (θ)	0	0
Restocking rate (α)	0	1

4.3.6 Model testing

The model described in this chapter is tested in three ways:

1. Running the deterministic and stochastic models with parameters that reflect the conditions in the Berriatua experiment (Parameter Set 1) and comparing the model results with the Berriatua results visually and with a chi squared test. This is repeated Parameter Set 2, the set of parameters estimated to be more suitable for longer term dynamics (described in section 4.3.6.1, results in section 4.4.1).
2. Running the deterministic and stochastic models over longer simulated time period (10 years) than seen in the Berriatua, with a larger flock size and for each of the parameter sets to investigate the impact on model output (described in section 4.3.6.2, results in section 4.4.2).
3. (As described in 2.3.4.3) - Running an uncertainty and a sensitivity analysis on the main parameters β, γ, q, ε, τ, μ, m, and α (described in section 4.3.6.3, results in section 4.4.3).

4.3.6.1 Comparison of simulation results to experimental results from the Berriatua study

A deterministic simulation of the model was run where one sheep was infected initially (day 0) and there were eight susceptible sheep. This was the average number of susceptible sheep used in the experiments done by Berriatua et al. (1999) and in all Berriatua experiments, only one infected sheep was introduced to a susceptible group. The time period of the simulation was 98 days, as the maximum number of days in the experiments was 98. The simulation was repeated for both parameter sets as calculated in section 4.3.5, with Parameter Set 1 reflecting the conditions in the Berriatua experiments and Parameter Set 2 reflecting conditions that might be seen in longer term scenarios. No control measures were used. The simulation was run deterministically in R and the equations solved numerically using the lsoda() function as part of the deSolve package (Soetaert et al., 2010) in R. The stochastic model was then run under the same conditions and for both parameter sets, each time with 500 repeats.

These results are compared visually with the results from five trials (Groups 1A, 1B, 2A, 2B and 2C) in the study by Berriatua et al. (1999) (Fig. 4.3, Fig. 4.4). The output compared is the prevalence of infection at the end of each week (the total number of infecteds and carriers in the flock on the final day of each week). The expected data were the median infected count each week across all five Berriatua experiments. A Pearson's Chi-squared test for count data was carried out using the "chisq.test" function from the "stats" (v3.6.1) package in R in order to test the null hypothesis that the model data and the experimental data from the Berriatua experiment were from the same distribution. This was assumed to be the case where the p value was greater than 0.01. The p value was calculated from the asymptotic chi-squared distribution of the test statistic.

4.3.6.2 Adjusting flock size and simulation time

The deterministic and stochastic models were run again under the same conditions and for both parameter sets, but for a simulated 10 year period (Fig.4.5 c & d) and then a further time for each parameter set for a 10 year period and with 200 sheep (Fig.4.5 g & h). The endemic equilibriums for the deterministic results were calculated using the "*runsteady"* function from the R package "rootSolve" (Soetaert, 2009). A Pearson's Chi-squared test for count data was carried out as described in section 2.3.5.1 between the median stochastic output and the deterministic output. The output measured was the number of carriers and infecteds at the end of each week.

4.3.6.3 Uncertainty and sensitivity analyses

The UA and SA were both run with respect to the output of most interest in this model, as suggested by Salteli et al. (2009), which in this case was the number of sheep acutely infected on a farm as a function of time (I(t) plus the number of carriers (C(t)). The UA and SA were both run once with respect to the Berriatua parameters and another time with respect to the parameters for longer term dynamics.

For the UA, LHS was used to generate 100 random parameter combinations per parameter of interest. When run with respect to the Berriatua parameter values, the parameters investigated were transmission rate (β), recovery rate (γ), transmission scaling rate for carriers (ε), proportion of acute infections that become carriers (*q)*,

and the rate at which carriers recover (τ). When running with respect to the parameters for longer term dynamics, the same parameters were investigated as well as the natural birth/death rate (μ), the disease mortality rate (m) and the restocking rate (α).

This was done in R using the randomLHS() function from the "lhs" package (Carnell, 2019) (correlations between parameters were not included). R_0 was also calculated for each parameter combination using equation 4.8. The probability density function (PDF) was assumed to be uniform for all parameters. The PDF range has been reported to be more influential in UA or SA results than the PDF distribution (Iman & Helton, 1988; Campolongo et al., 2000) and so it was thought that it would be useful to examine results from a number of different PDF ranges. Latin hypercube sampling was carried out three times for both parameter sets, to allow for different PDF ranges to be used. For all parameters, the PDF range was 10% above and below the baseline parameter value in the first LHS, 50% in the second and 100% in the third. The one exception to this rule was the PDF range for the restocking rate (α) in Parameter Set 2. As the baseline value for the restocking rate (α) was the maximum value possible for the restocking rate (α =1), it was decided that the PDF range for all three iterations of LHS would be from 0 to 1 so that only parameter values of interest were explored (<1) and a wide range of values were investigated, particularly as α was not estimated using data from the literature. For each of the three LHS iterations, the model was run in R deterministically 100 times, once for each group of generated parameters. Each simulation was run for 3650 simulated days (10 simulated years in total).

To identify which correlation test for the sensitivity analysis would be most suitable, the relationship between each parameter of interest and the output (to test for monotonicity) was investigated, by running simulations of the R deterministic model, using the baseline values for all parameters except the parameter of interest, which was varied from 0 to 1 by 0.001 (a OAT approach). The specific output that was investigated was the fraction of the flock infected (both acute infections and carriers) at time step 3650 when a single sheep was infected and 8 sheep were susceptible at time step 0. This was carried out for all parameters used in the LHS for longer term dynamics ((μ ,β, γ, ε, q. τ, m and α) and for 3650 time steps.

The partial rank correlation coefficient (PRCC) was selected as the most suitable correlation test to further investigate the relationship between the model inputs and outputs, where this relationship was confirmed to be monotonic (Marino et al., 2008). The results from the LHS where the PDF ranges are 100% above and below the baseline values for the parameters of interest were used in the PRCC for both parameter sets. The PRCCs between each of the parameters and the fraction of sheep that were infected or carriers at time step 3650 (final time step) were calculated using the pcc() function from the sensitivity package (Ioss et al., 2018) with one thousand bootstrap replicates and a 0.95 confidence level of the bootstrap confidence intervals. The PRCCs were also calculated using the epi.prcc() function from the "epiR" package (Stevenson et al., 2018) with a two-sided test, as this function also calculates the *p*-value for each of the PRCCs.

Where the monotonicity tests revealed a non-monotonic relationship between model inputs and outputs, a Kruskal-Wallis rank sum test was used to investigate the changes in the distribution of model output across the range of parameter input values as described in Helton & Davis (2002). Where the p value is less than 0.05, the parameter may have a non-monotonic relationship with the model output. The parameter input values were ranked in order of size and then grouped (firstly into two groups of 50 and then a second time into 10 groups of 10) and the kruskal.test() function from the "stats" package in R was used to perform the test for each set of groups.

4.4 RESULTS

4.4.1 Comparison of simulation results to experimental results from the Berriatua study

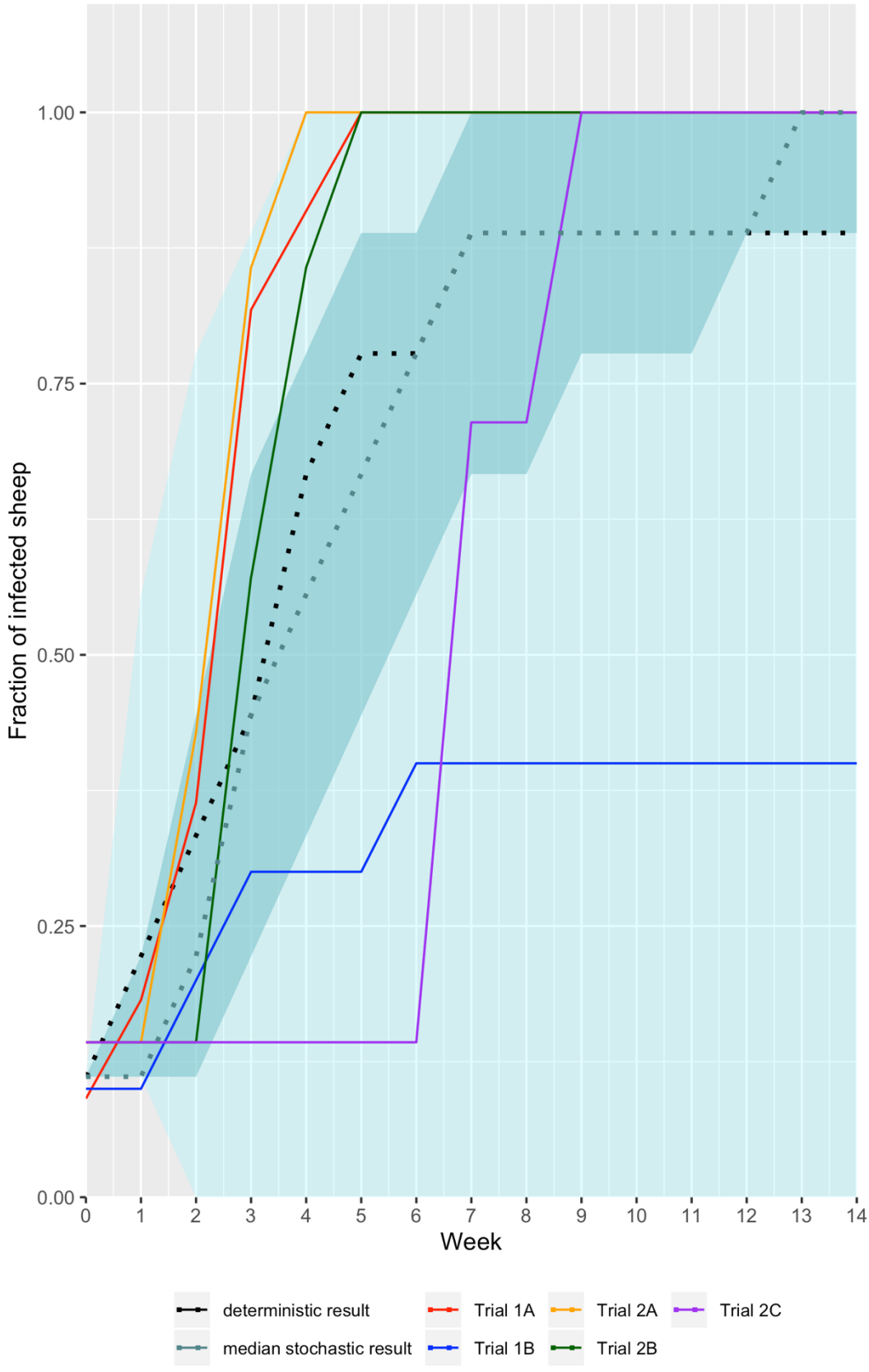
The raw data from Trials 1A, 1B, 2A, 2B, and 2C from Berriatua et al. (1999) are plotted with the results from the stochastic and deterministic runs of the model (Fig. 4.3), while the median, interquartile range and 2.5-97.5 percentiles of all five Berrituata trials are plotted with the same model simulation results on a separate figure (Fig. 4.4).

For the set of model parameters that match the conditions of the Berriatua experiment (Parameter Set 1), the null hypothesis that the model output and the experimental data were from the same distribution was accepted for both the deterministic (χ^2= 10.085, df = 14, p = 0.756) and stochastic (χ^2= 9.4236, df = 14, p = 0.803) models. The median result for the stochastic simulation (n = 500) and the deterministic result mostly lie within the upper and lower quartiles of the experimental results from Berriatua et al. (1999) and where they do not, the stochastic median lies completely and the deterministic result mostly within the 2.5th and 97.5th percentiles (Fig. 4.4a).

However, for the set of model parameters that were estimated with longer term dynamics in mind (Parameter Set 2), the null hypothesis that the model output and the experimental data were from the same distribution was rejected for both the deterministic (χ^2= 66.154, df = 14, p < 0.001) and stochastic models (χ^2= 61.303, df = 14, p < 0.001), although, the deterministic and stochastic outputs themselves were thought to be from the same distribution (χ^2= 1.1659, df = 14, p = 1.000). The deterministic result did not lie within the 2.5th and 97.5th percentiles of the experimental results from Berriatua et al. (1999) and overestimated the rate at which sheep became infected in comparison to the experimental results. However, once an endemic equilibrium was reached the fraction of flock infected in the deterministic output was the same as the median result from the experimental data (Fig. 4.3b, Fig. 4.4b). The median stochastic result (n= 500) also overestimated the rate at which sheep became infected in comparison to the experimental results, however, there was

some overlap between the median and quartiles from the stochastic output and the quartiles of the experimental data after the first 2 simulated weeks (Fig. 4.4b).

(a)


1.00
0.75
0.50
0.25
0.00
Fraction of infected sheep
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
Week
deterministic result
median stochastic result
Trial 1A
Trial 1B
Trial 2A
Trial 2B
Trial 2C

(b)

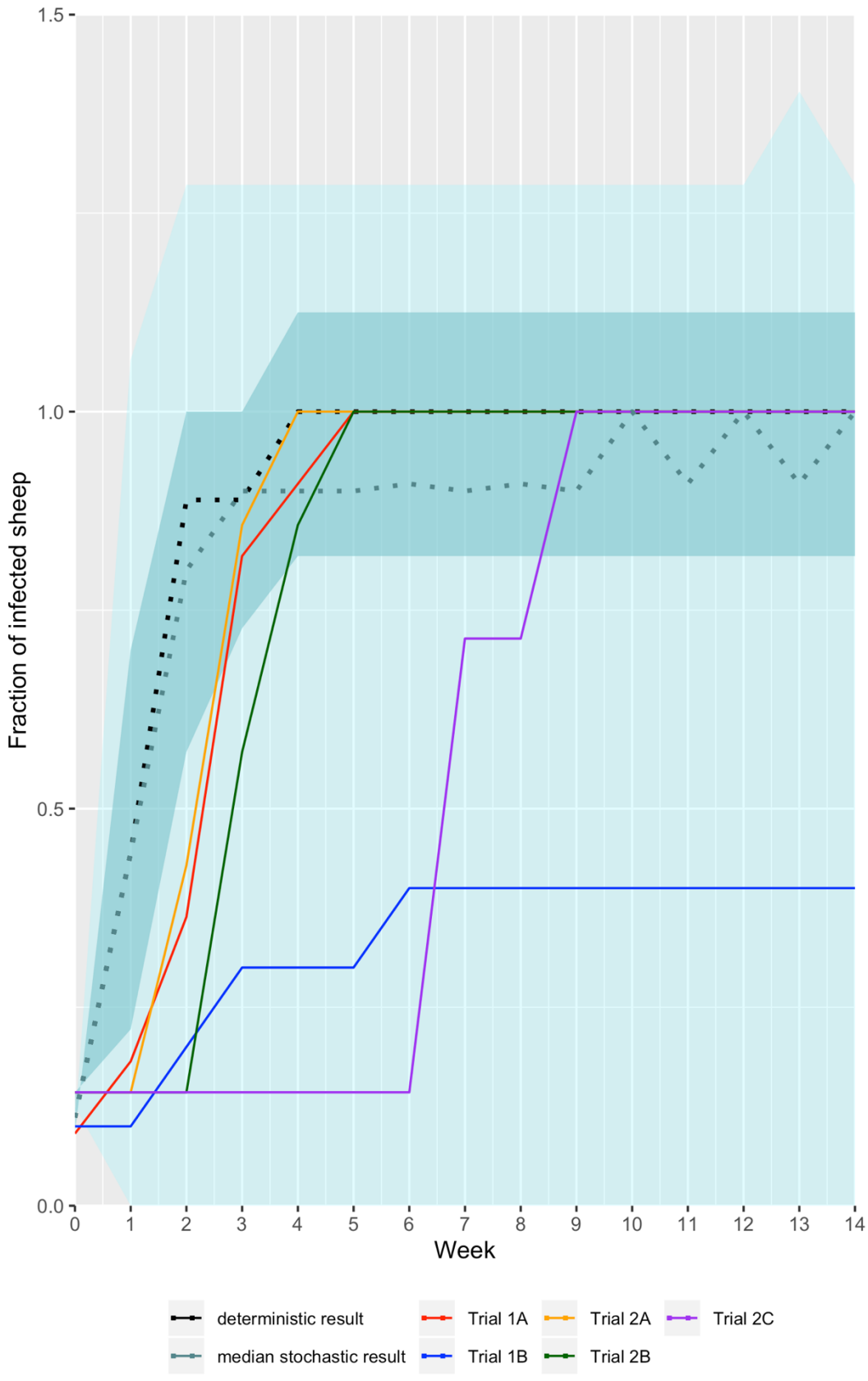
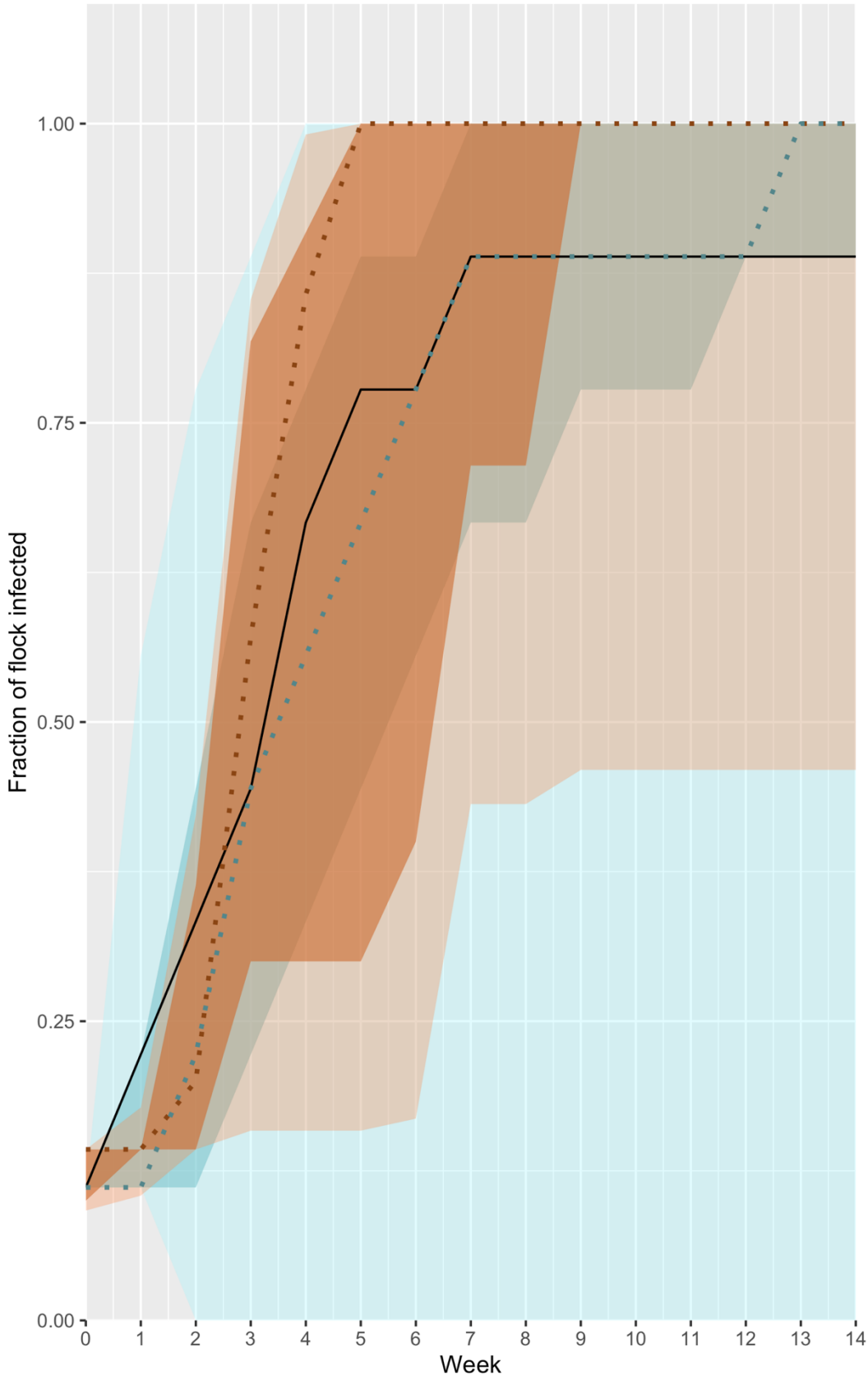

1.5
1.0
0.5
0.0
Fraction of infected sheep
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
Week
deterministic result
median stochastic result
Trial 1A
Trial 1B
Trial 2A
Trial 2B
Trial 2C

Fig. 4.3. Fraction of flock infected with sheep scab over a period of 14 weeks in experimental data and in model simulations after introduction of one index case of scab. (a) The simulation results when Parameter Set 1 were used; **(b)** the results when Parameter Set 2 were used.
The results are given as integers of sheep per week (hence the step-like nature) and indicate the number of infected sheep at the end of each week divided by the number of sheep in the flock (the end-of-week prevalence). The unbroken lines are the results from five trials described in the Berriatua et al. (1999) paper. The dashed lines are results from the model simulations; the black line is the deterministic result and blue line is the median stochastic result (n= 500). The dark blue shaded area is the interquartile range of the stochastic results and the light blue shaded area is the 2.5-97.5th percentile range of the stochastic results. In the simulations, there was one infected sheep and eight susceptible sheep on day 0. In the experimental data, there was one infected sheep and a range of 6-10 susceptible sheep on day 0.

(a)


1.00
0.75
0.50
0.25
0.00
Fraction of flock infected
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
Week

(b)

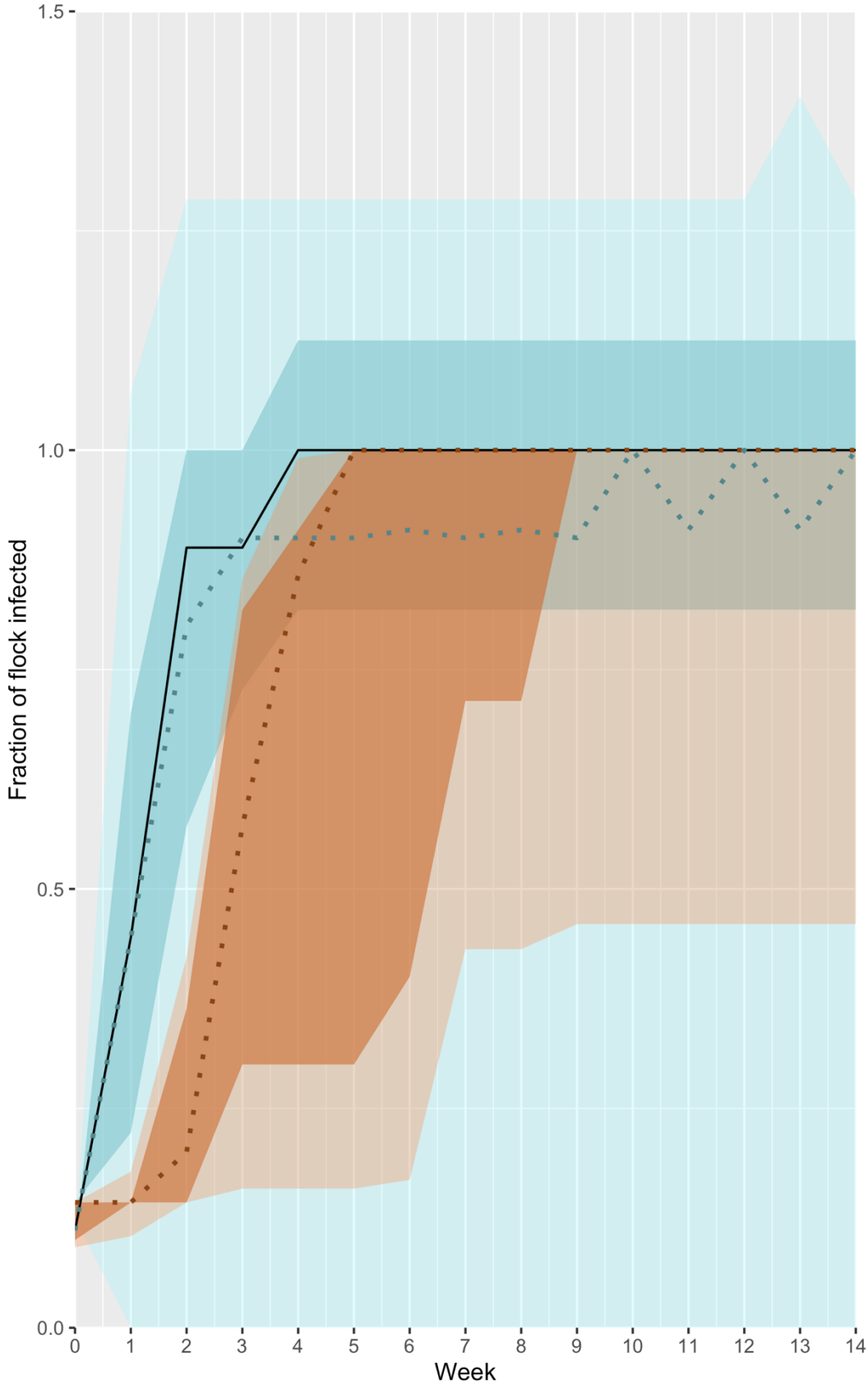

1.5
1.0
0.5
0.0
Fraction of flock infected
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
Week

Fig. 4.4. Fraction of flock infected with sheep scab each week over a period of 14 weeks in summarised experimental data and in model simulations after introduction of one index case of scab. (**a)** The simulation results when Parameter Set 1 were used; **(b)** the results when Parameter Set 2 were used.
The results are given as integers of sheep per week (hence the step-like nature of the graph) and indicate the number of infected sheep at the end of each week divided by the number of sheep in the flock (the end-of-week prevalence). Results from trials 1A, 1B, 2A, 2B and 2C in the Berriatua et al. (1999) study were summarised (orange), as were the results from 500 runs of the stochastic version of the within-farm SIDT model of sheep scab (blue). The darker shaded areas indicate the upper and lower quartiles, the lighter shaded areas the 2.5^{th} and 97.5^{th} percentiles and the coloured lines show the median. The black line is the result from the deterministic version of the model. In the simulations, there was one infected sheep and eight susceptible sheep on day 0. In the experimental data, there was one infected sheep and a range of 6-10 susceptible sheep on day 0.

4.4.2 Adjusting flock size and simulation time

The epidemic of scab reaches both its peak and endemic equilibrium sooner when Parameter Set 2 is used in the model compared to when Parameter Set 1 is used, regardless of flock size and for both the deterministic and stochastic models (Fig 4.3, Fig. 4.4, Table 4.5). For both parameter sets, the epidemic reaches its peak sooner than when the flock size is 200 than when it is 9 (Fig 4.5, Fig. 4.6). However, it reaches endemic equilibrium sooner when the flock size is 9 compared to when it is 200 (Table 4.4).

When endemic equilibrium is reached there are a higher proportion of carriers than infecteds and no individuals in any of the other disease states for both flock sizes and both parameter sets and the numbers of individuals in each disease state is the same between parameter sets with a 9 sheep flock. However, with a 200 sheep flock, there are slight differences in the numbers of whole sheep at endemic equilibrium in each disease state when different parameter sets are used (Table 4.4).

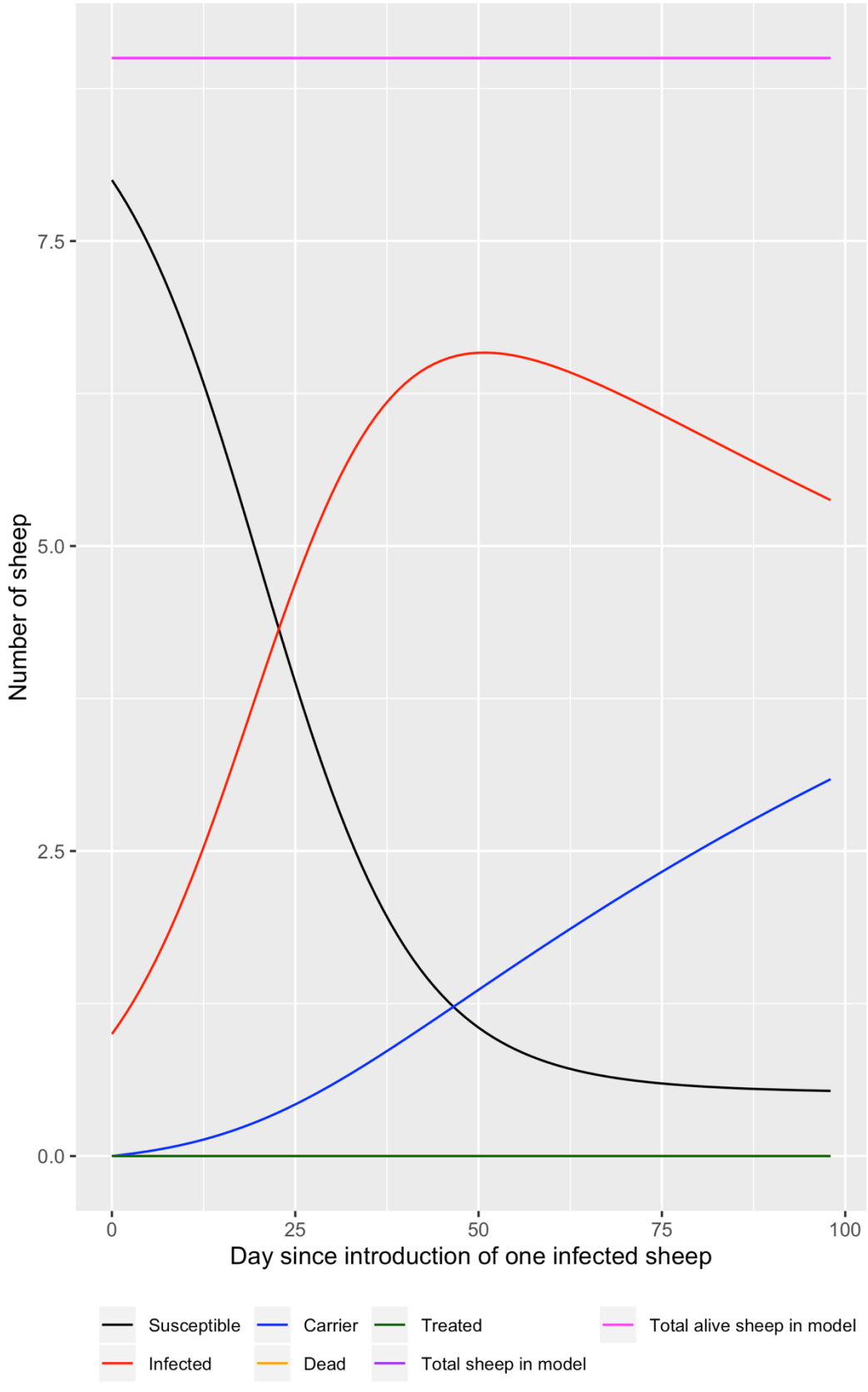
No disease deaths occur when Parameter Set 1 is used since the mortality rate is 0, however, disease deaths occur at a continuous low level when Parameter Set 2 is used (Fig 4.5), with 1151 sheep and 50 sheep dying from scab in total over a period of 10 years when a maintaining a constant flock size of 200 and 9 respectively.

When the model is run stochastically (n = 500) over a period of 10 years the median stochastic output converges with the deterministic output and it was shown to be from the same distribution for both Parameter Set 1 (χ^2= 9.7408, df = 521, p > 0.01) and Parameter Set 2 (χ^2= 9.7378 df = 521, p > 0.01). Once the endemic equilibrium for the deterministic output has been reached, the majority of the flock in the stochastic output still remains infected or a carrier for the remainder of the simulation, although there is much more variation in the output when there are only 9 sheep in the flock compared to 200 (Fig. 4.6).

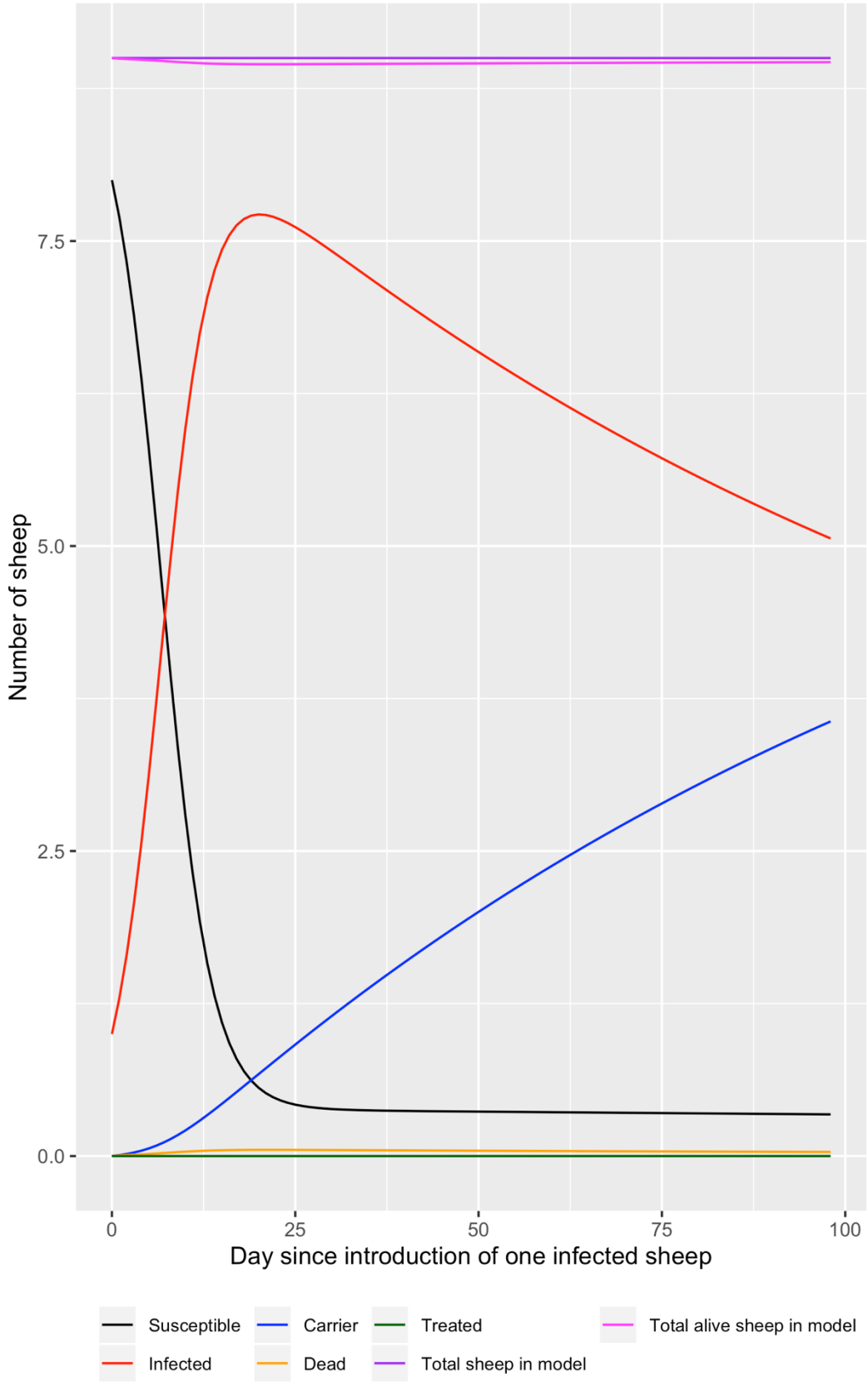
Table 4.4 The endemic equilibrium and final size from four deterministic simulations of the SICTD scab model, with each simulation using a different combination of flock size and parameter set. Each simulation was run for a simulated 10 years and the "*runsteady"* function from the R package "rootSolve" (Soetaert, 2009) was used to calculate the endemic equilibrium. The results are compared to the final size at the end of the 14 weeks (which is the time period used in the model simulations in section 4.3.6.1).

	Parameter Set 1						Parameter Set 2					
	9 sheep flock			200 sheep flock			9 sheep flock			200 sheep flock		
	Final size after 14 weeks	Solution for endemic equilibrium	Endemic equilibrium for whole numbers of sheep	Final size after 14 weeks	Solution for endemic equilibrium	Endemic equilibrium for whole numbers of sheep	Final size after 14 weeks	Solution for endemic equilibrium	Endemic equilibrium for whole numbers of sheep	Final size after 14 weeks	Solution for endemic equilibrium	Endemic equilibrium for whole numbers of sheep
S	0.53	0.4520531	0	0.5132135	0.452053	0	0.3415672	0.2551490 5	0	0.3364853	0.2551490	0
I	5.38	1.6312095	2	112.92603	38.079782	38	5.062201	1.8619073 3	2	112.07880	42.528579 7	43
C	3.09	6.9167374	7	86.56075	161.468165	161	3.5626097	6.8706407 7	7	86.26344	156.9352569	157
D	0	0	0	0	0	0	0.0336223 8	0.7481992 0	0	0.7481992 0	0.2810145	0
P	0	0	0	0	0	0	0	0	0	0	0	0
Time	98	2006.627	381	98	2078.765	745	98	1953.379	372	98	2594.766	719

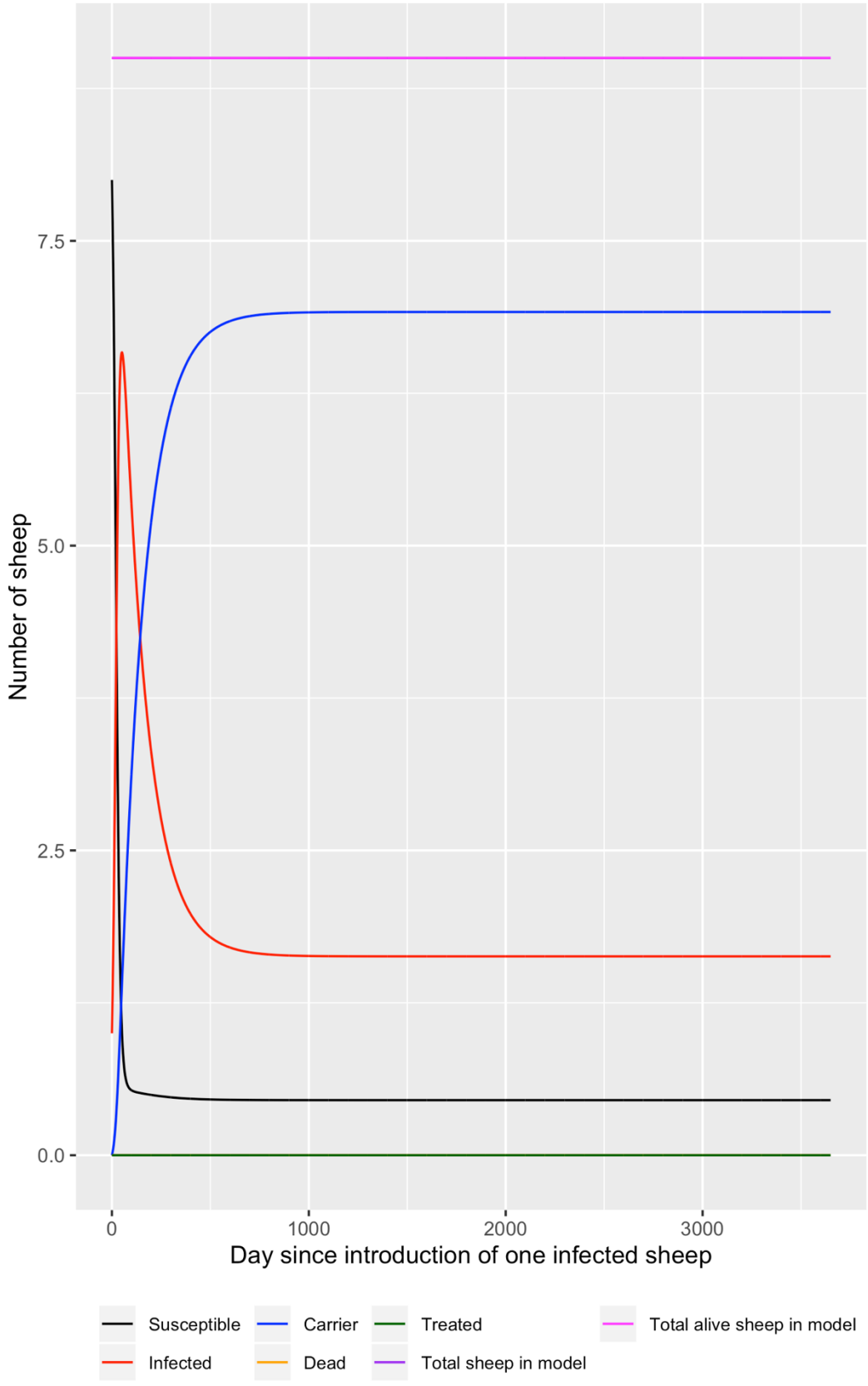
(a)


7.5
5.0
2.5
0.0
Number of sheep
0
25
50
75
100
Day since introduction of one infected sheep
Susceptible
Carrier
Treated
Total alive sheep in model
Infected
Dead
Total sheep in model

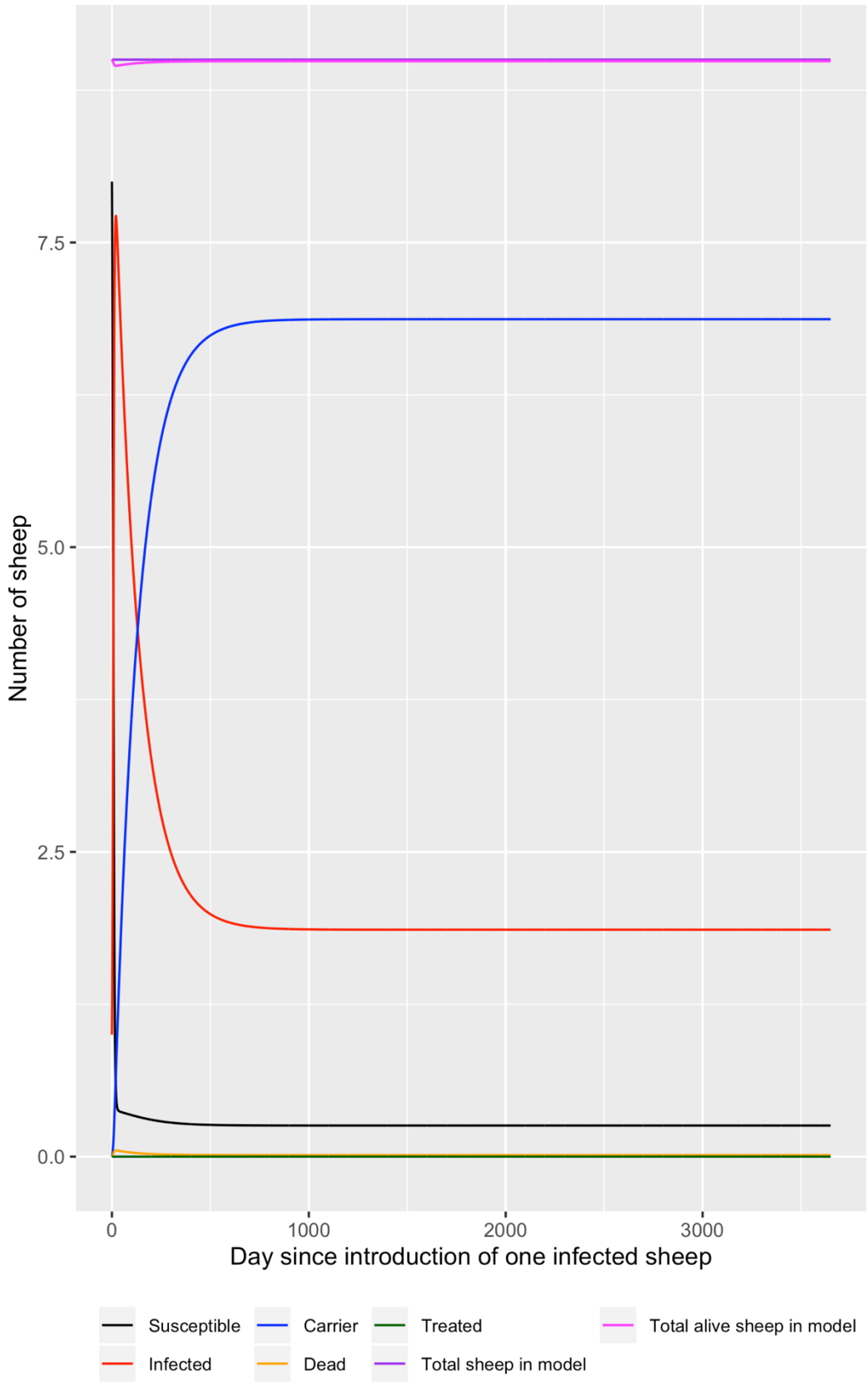
(b)


Number of sheep
7.5
5.0
2.5
0.0
0
25
50
75
100
Day since introduction of one infected sheep
Susceptible
Infected
Carrier
Dead
Treated
Total sheep in model
Total alive sheep in model

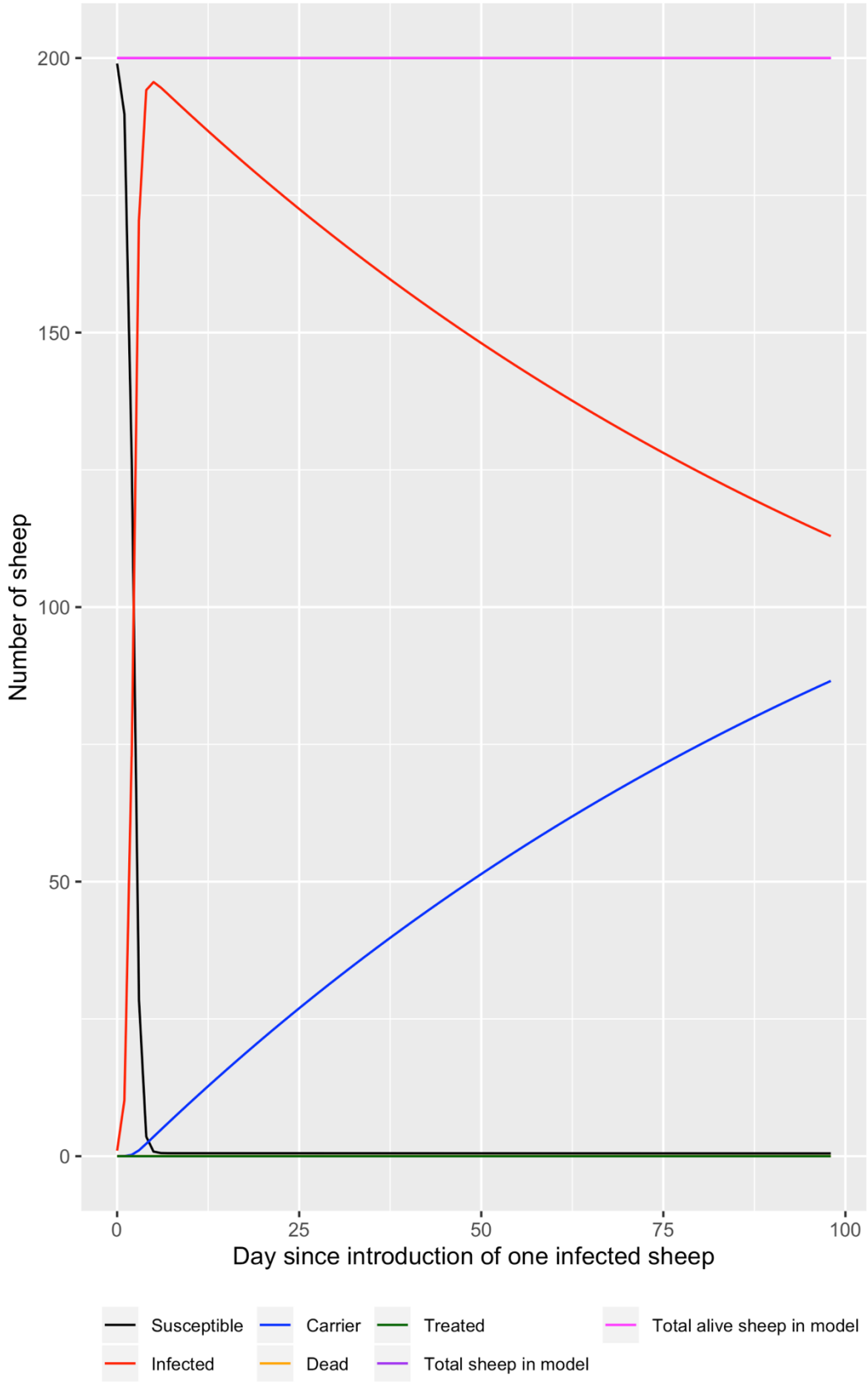
(c)


7.5
5.0
2.5
0.0
Number of sheep
0
1000
2000
3000
Day since introduction of one infected sheep
Susceptible
Carrier
Treated
Total alive sheep in model
Infected
Dead
Total sheep in model

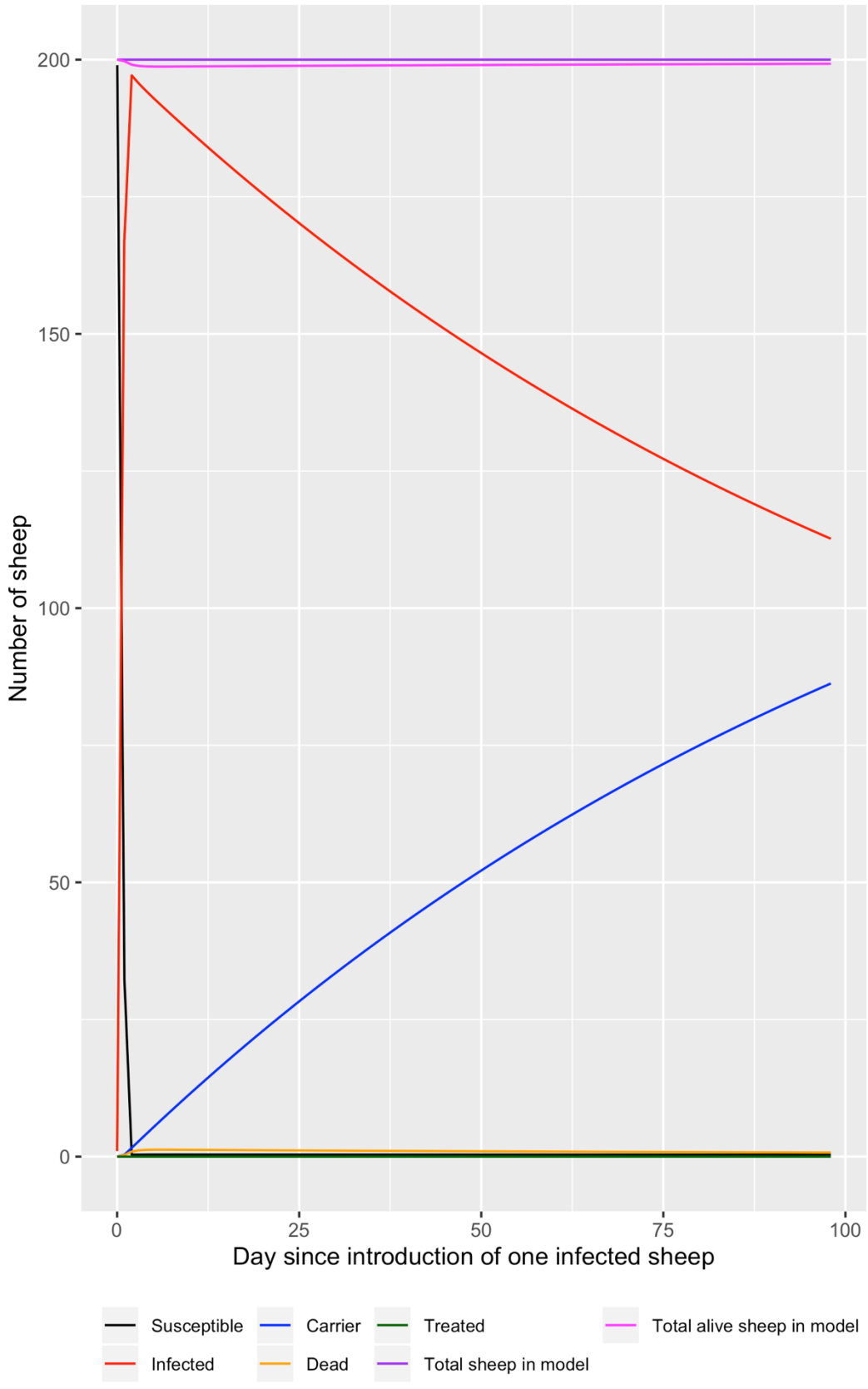
(d)


Number of sheep
7.5
5.0
2.5
0.0
0
1000
2000
3000
Day since introduction of one infected sheep
Susceptible
Infected
Carrier
Dead
Treated
Total sheep in model
Total alive sheep in model

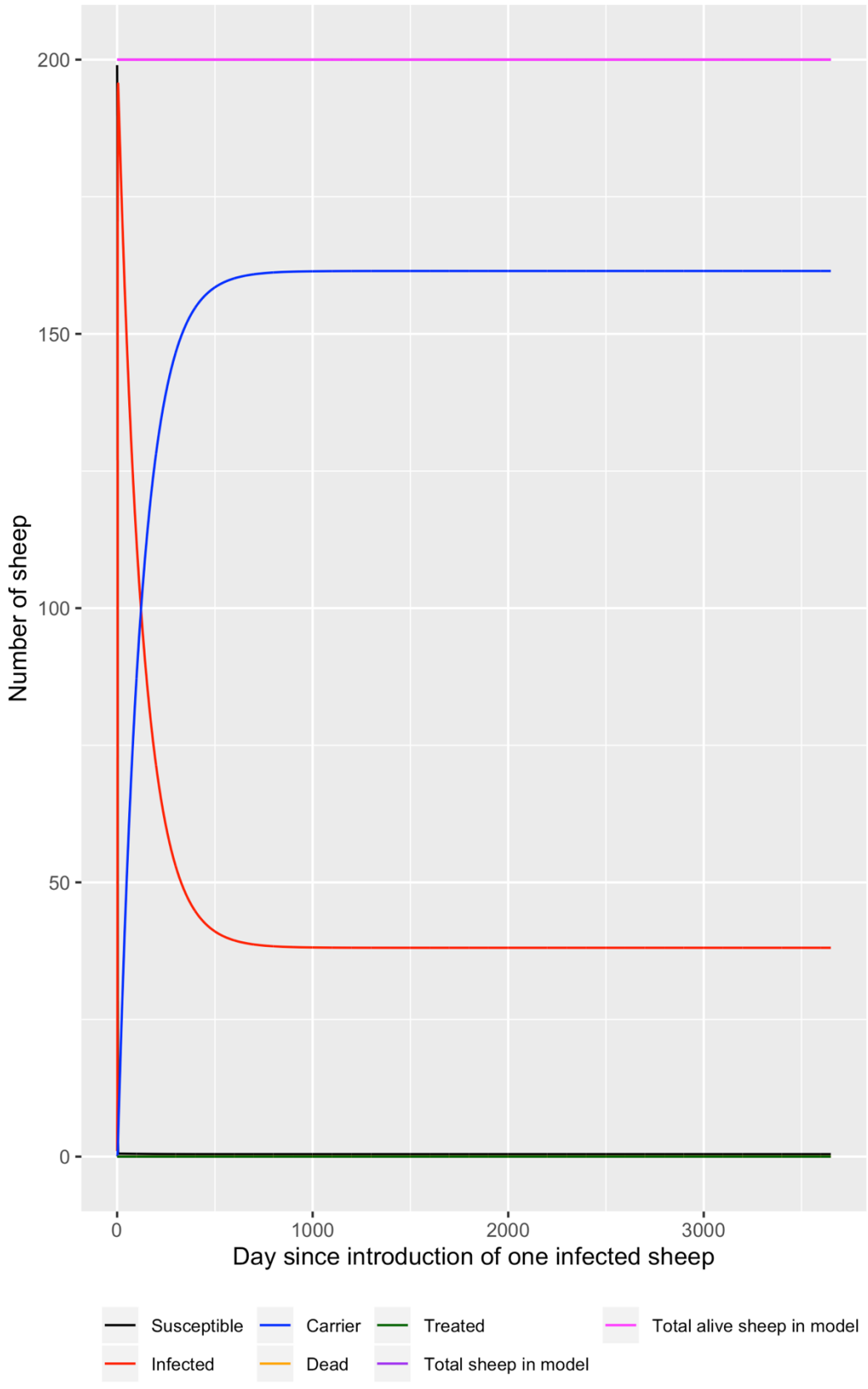
(e)


200
150
100
50
0
Number of sheep
0
25
50
75
100
Day since introduction of one infected sheep
Susceptible
Carrier
Treated
Total alive sheep in model
Infected
Dead
Total sheep in model

(f)


200
150
100
50
0
Number of sheep
0
25
50
75
100
Day since introduction of one infected sheep
Susceptible
Carrier
Treated
Total alive sheep in model
Infected
Dead
Total sheep in model

(g)


200
150
100
50
0
Number of sheep
0
1000
2000
3000
Day since introduction of one infected sheep
Susceptible
Carrier
Treated
Total alive sheep in model
Infected
Dead
Total sheep in model

(h)

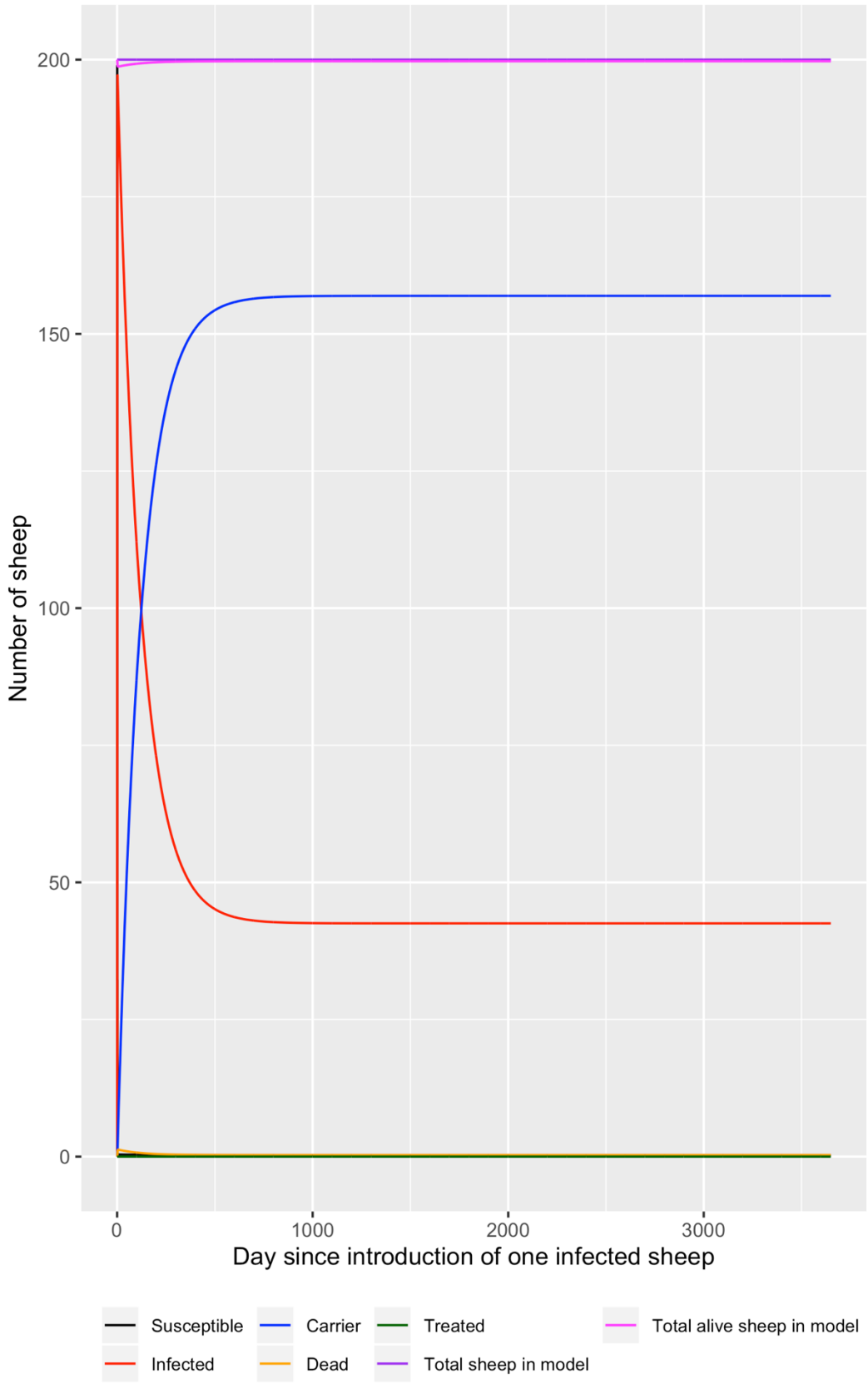
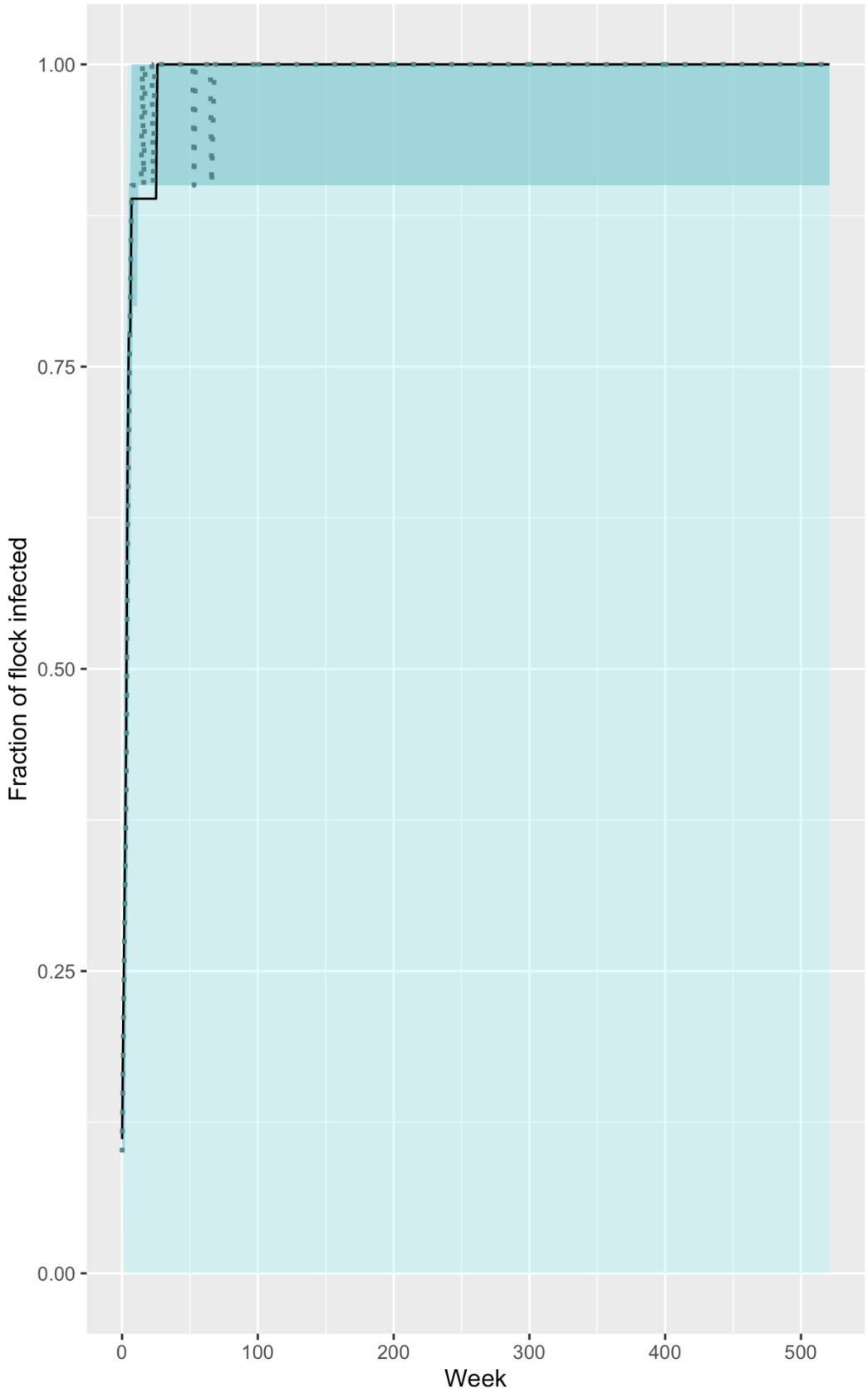
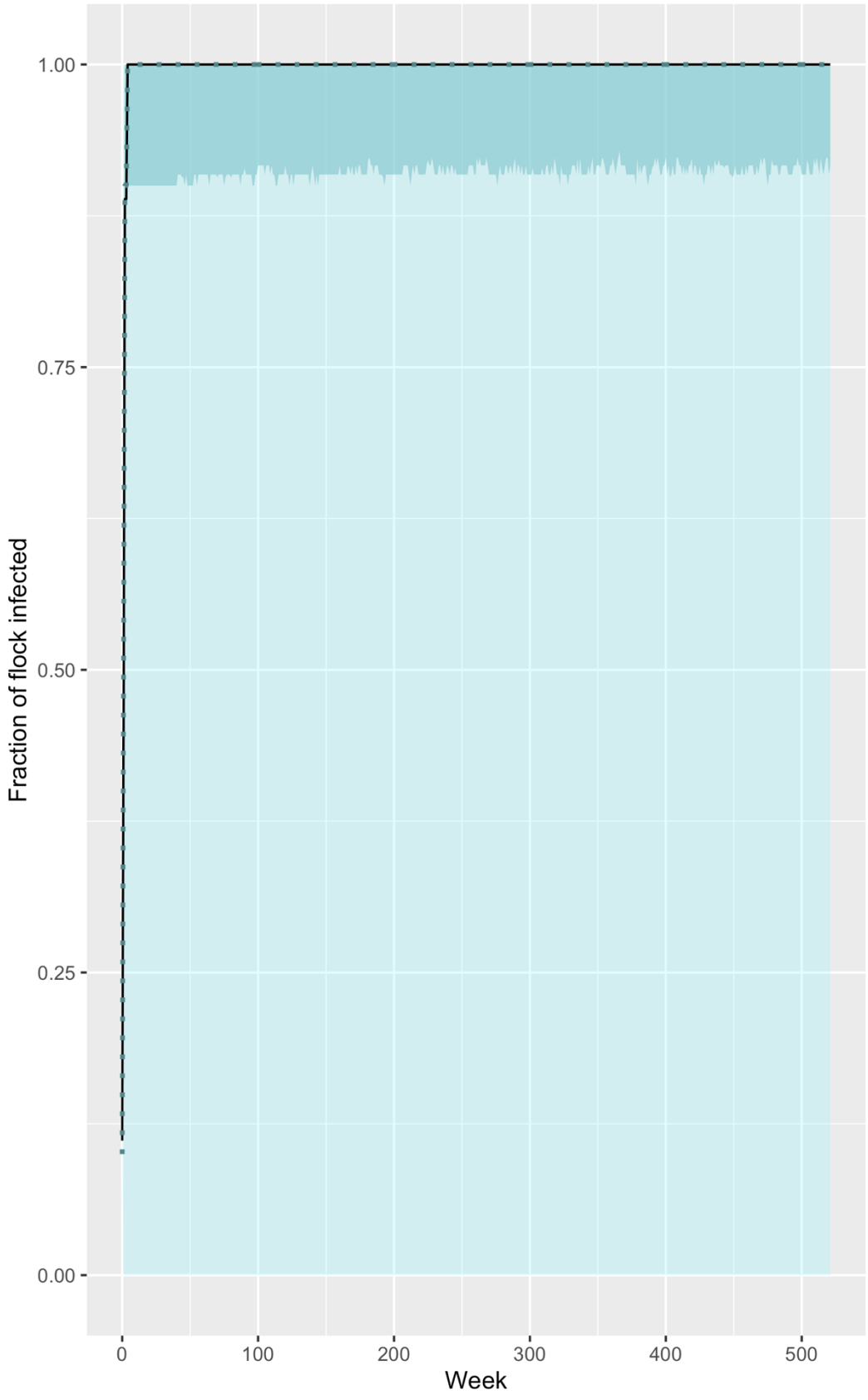

200
150
100
50
0
Number of sheep
0
1000
2000
3000
Day since introduction of one infected sheep
Susceptible
Carrier
Treated
Total alive sheep in model
Infected
Dead
Total sheep in model

Fig. 4.5 The number of sheep in each disease state in deterministic outputs from a SICTD model of sheep scab with different parameter sets, flock sizes and simulation times. "Total sheep in model" includes those which have died from having scab and will be restocked (S+I+C+T+D), whereas "Total alive sheep" only includes counts from disease states where sheep are alive (S + I + C + T). The deterministic model was run six times, for different lengths of time, numbers of sheep and parameter sets : Parameter Set 1- those that reflect the conditions in experiments by Berriatua et al. (1999) and Parameter Set 2- those that were estimated with longer term dynamics in mind. **(a)** Simulation using Parameter Set 1 with 8 susceptible and 1 infected sheep at the start and run for a total of 98 days, **(b)** Simulation using Parameter Set 2 with 8 susceptible and 1 infected sheep at the start and run for a total of 98 days, **(c)** Simulation using Parameter Set 1 with 8 susceptible and 1 infected sheep at the start and run for a total of 10 years, **(d)** Simulation using Parameter Set 2 with 8 susceptible and 1 infected sheep at the start and run for a total of 10 years, **(e)** Simulation using Parameter Set 1 with 199 susceptible and 1 infected sheep at the start and run for a total of 98 days, **(f)** Simulation using Parameter Set 2 with 199 susceptible and 1 infected sheep at the start and run for a total of 98 days **(g)** Simulation using Parameter Set 1 with 199 susceptible and 1 infected sheep at the start and run for a total of 10 years, **(h)** Simulation using Parameter Set 2 with 199 susceptible and 1 infected sheep at the start and run for a total of 10 years

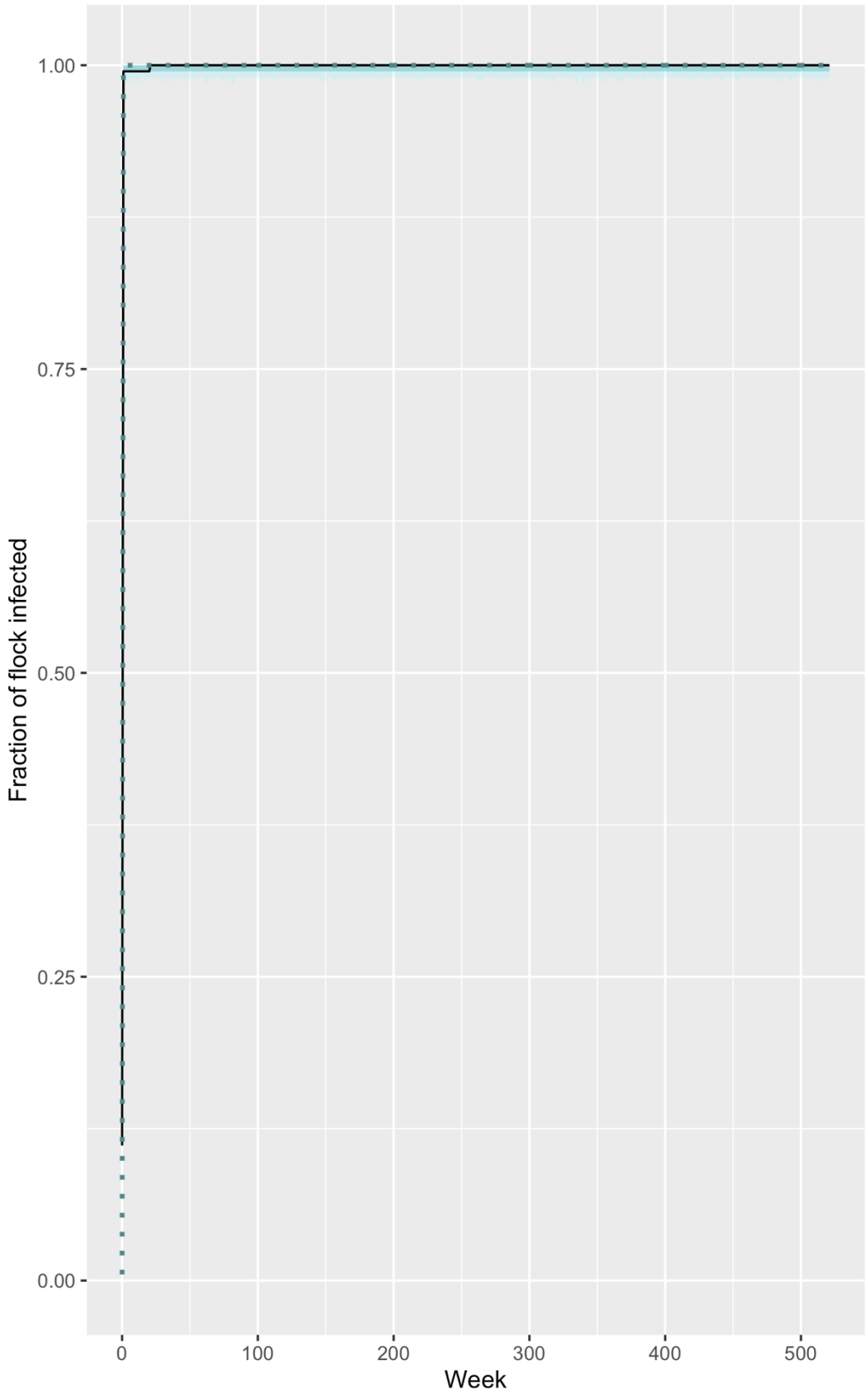
(a)


1.00
0.75
0.50
0.25
0.00
Fraction of flock infected
0
100
200
300
400
500
Week

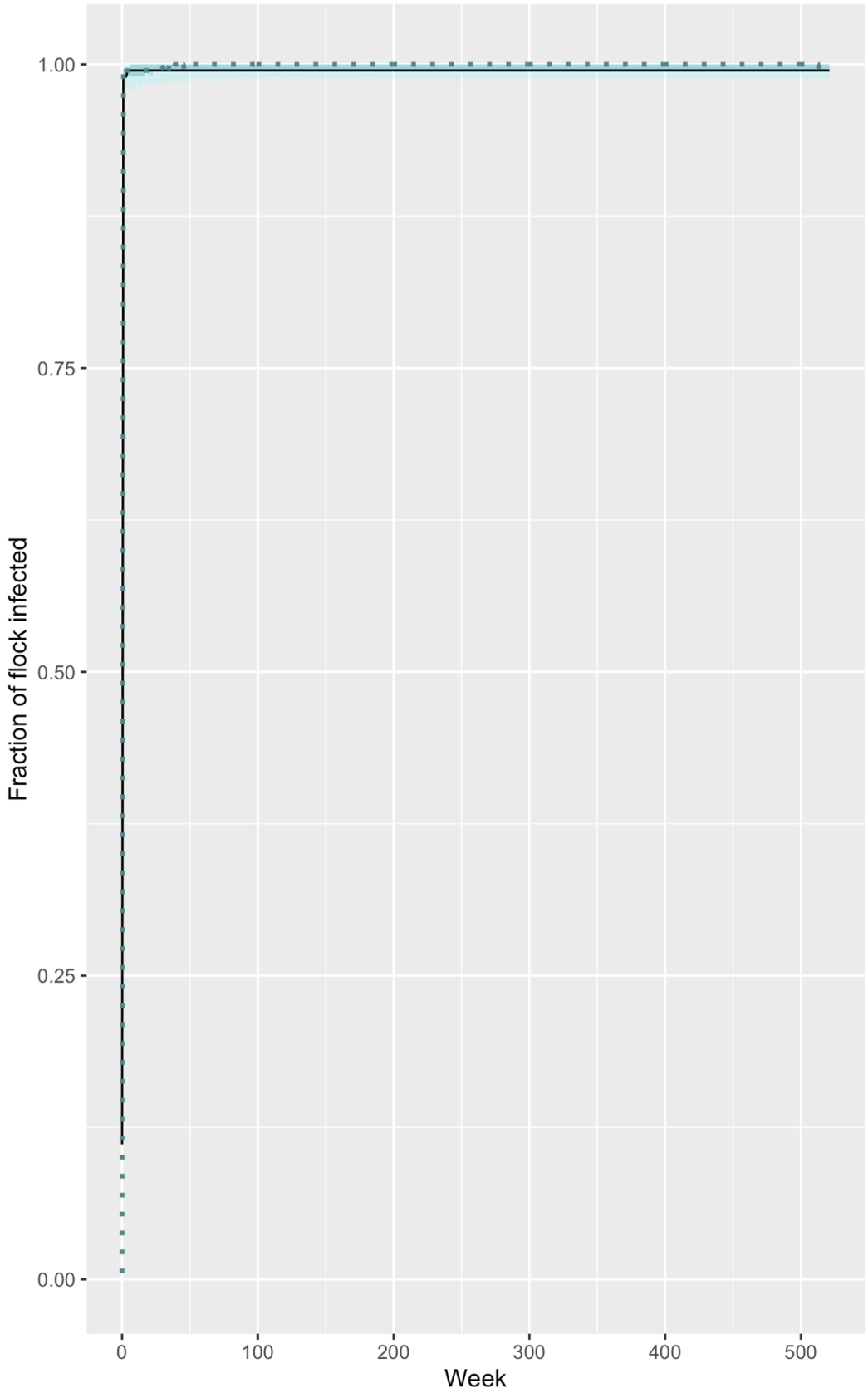
(b)


1.00
0.75
0.50
0.25
0.00
Fraction of flock infected
0
100
200
300
400
500
Week

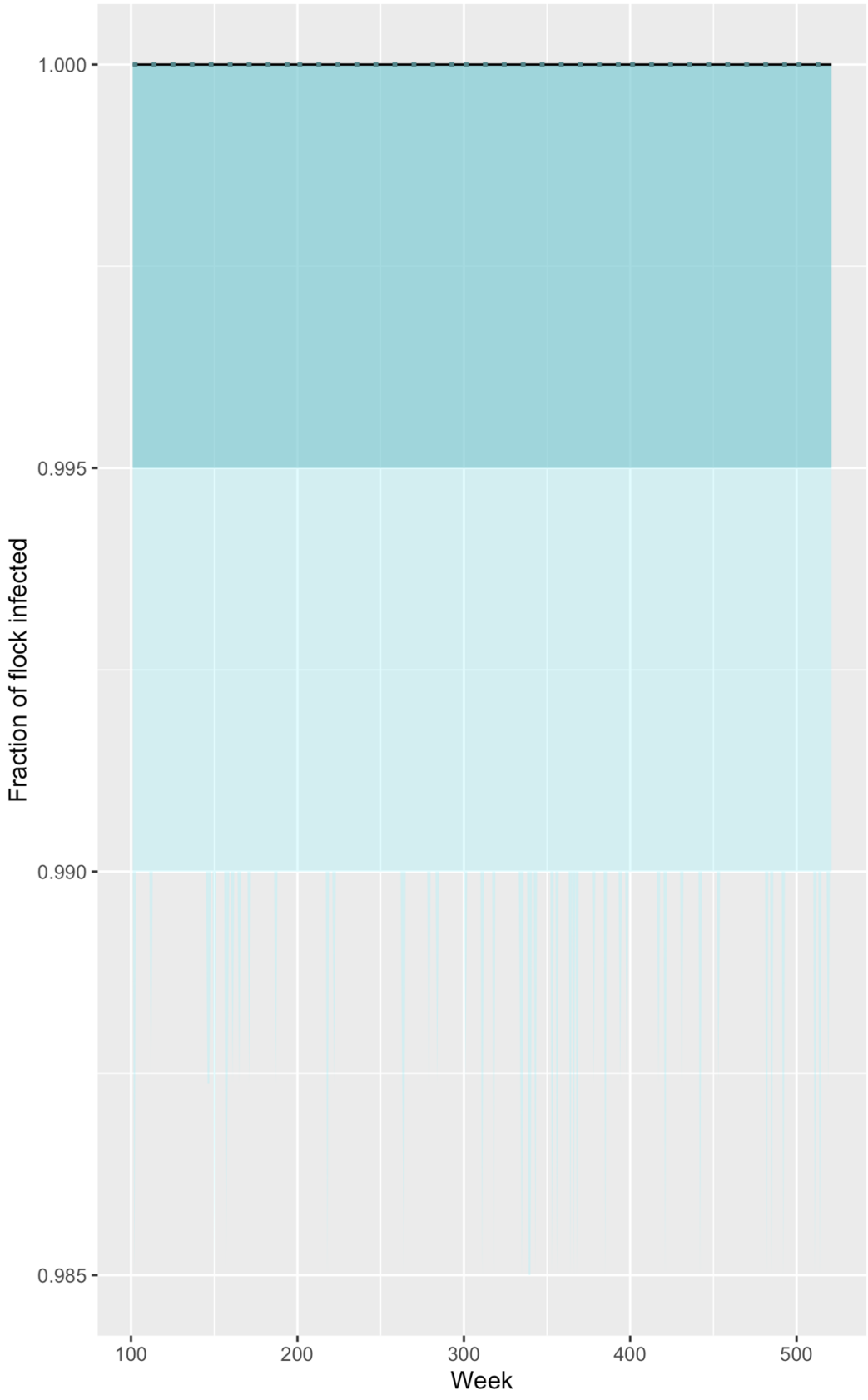
(c)


1.00
0.75
0.50
0.25
0.00
Fraction of flock infected
0
100
200
300
400
500
Week

(d)


1.00
0.75
0.50
0.25
0.00
Fraction of flock infected
0
100
200
300
400
500
Week

(e)


1.000
0.995
0.990
0.985
Fraction of flock infected
100
200
300
400
500
Week

(f)

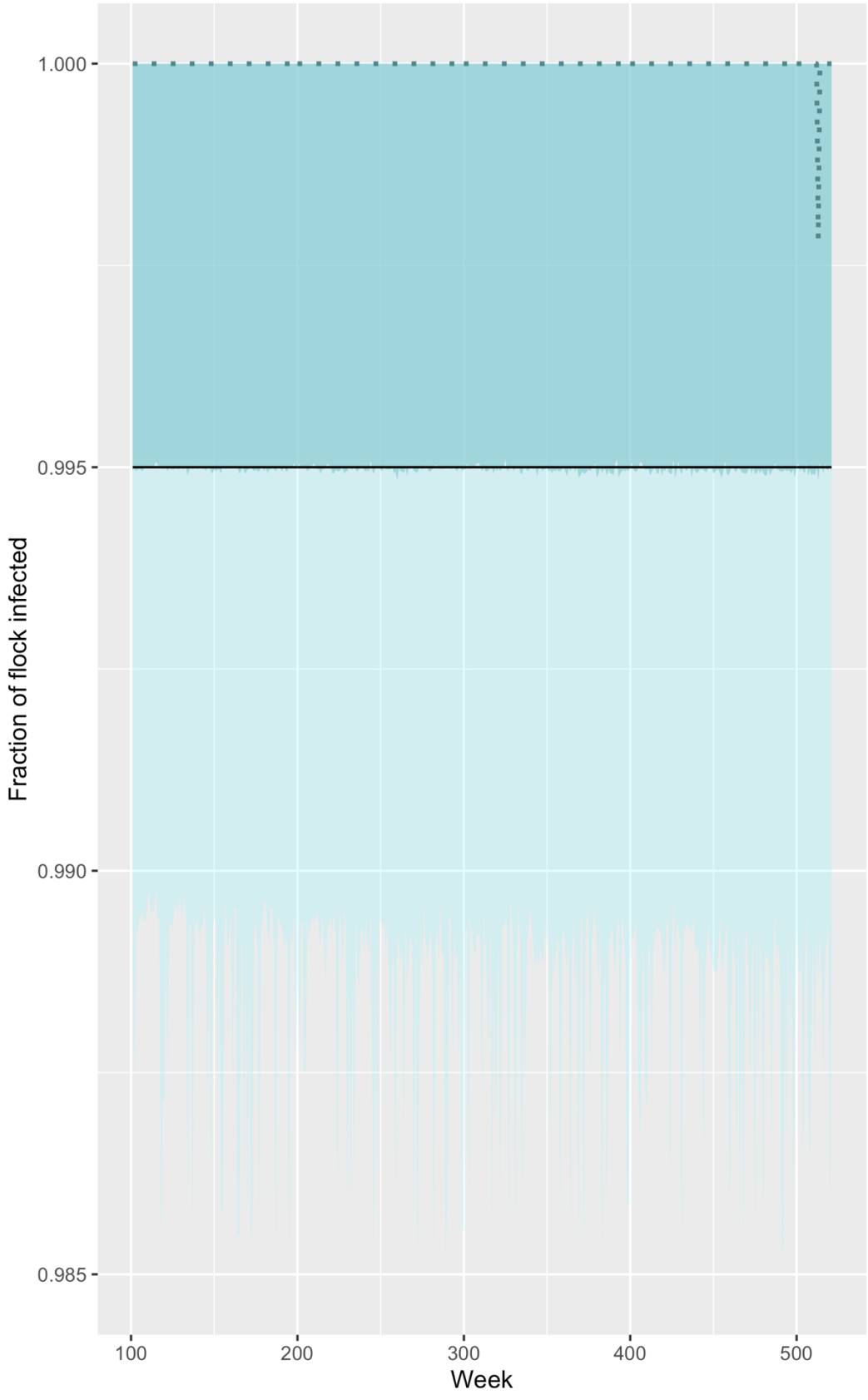

1.000
0.995
0.990
0.985
Fraction of flock infected
100
200
300
400
500
Week

Fig. 4.6 The fraction of infecteds and carriers at the end of each week in a deterministic and stochastic model of scab over a period of 10 years. The stochastic model was run 500 times and the median (blue dotted line), interquartile range (dark blue shading) and the 2.5-97.5th percentile range (light blue shading) are given. The deterministic result is given by the black line. **(a)** Parameter Set 1, initial conditions: 8 susceptible and one infected sheep **(b)** Parameter Set 2, initial conditions: 8 susceptible and one infected sheep, **(c)** Parameter Set 1, initial conditions: 199 susceptible and one infected sheep, **(d)** Parameter Set 2, initial conditions: 199 susceptible and one infected sheep, **(e)** same result as (c) shown after the first 100 weeks have passed, **(f)** same result as (d) shown after the first 100 weeks have passed.

4.4.3 Uncertainty and Sensitivity analysis of parameters

4.4.3.1 Latin hypercube sampling

A summary of the parameter values selected in three iterations of LHS is given, where a PDF range 10%, 50%, and 100% (Table 4.5) above and below the baseline parameter values for β, γ, ε, *q and* τ for both parameter sets and for μ and *m* from Parameter Set 2. The restocking rate (α) from Parameter Set 2 had a PDF range of 0 to 1. For the iteration with PDF range 10% for both parameter sets, no values of R_0 were below 1 or above 5. For the 50% PDF range, 7% of R_0 values were below 1 and 1% were above 5 for Parameter Set 1, while for Parameter Set 2, 2% of R_0 values were below 1 and 1% were above 5. For the 100% PDF range, 25% of R_0 values were below 1 and 27% were above 5 for Parameter Set 1 and 22% of R_0 values were below 1 and 14% were above 5 for Parameter Set 1.

Table 4.5. Summary data (n=100) for parameter combinations calculated using LHS in an uncertainty analysis of a within-farm SICTD transmission model of sheep scab. There are six parameter combinations in total: for both parameter sets estimated in section 4.5.6 there are three different combinations of parameters, each with a different probability distribution range for the parameters as indicated in the table heading (excluding the restocking rate, α, which had a range from 0 to 1 in every parameter combination). Parameters that had a baseline value of 0 were excluded from the LHS. The values for β and R_0 are rounded to two significant figures and the values for all other parameters are given as fractions with a numerator of 1 and the denominator rounded to the nearest whole number. All units are day^{-1} other than for R_0 which has no units.

Parameter Set 1

Probability distribution 10% above and below baseline parameter values						
	β	γ	ε	q	τ	R_0
Baseline value in model	1.2×10^{-2}	$\frac{1}{77}$	$\frac{1}{3}$	$\frac{1}{2}$	$\frac{1}{653}$	2.2
Minimum value	1.1×10^{-2}	$\frac{1}{85}$	$\frac{1}{3.3}$	$\frac{1}{2.2}$	$\frac{1}{725}$	1.8
1st Quartile	1.1×10^{-2}	$\frac{1}{81}$	$\frac{1}{3.1}$	$\frac{1}{2.1}$	$\frac{1}{687}$	2.1
Median	1.2×10^{-2}	$\frac{1}{77}$	$\frac{1}{3}$	$\frac{1}{2}$	$\frac{1}{653}$	2.2
Mean	1.2×10^{-2}	$\frac{1}{77}$	$\frac{1}{3}$	$\frac{1}{2}$	$\frac{1}{653}$	2.2
3rd Quartile	1.2×10^{-2}	$\frac{1}{73}$	$\frac{1}{2.8}$	$\frac{1}{1.9}$	$\frac{1}{622}$	2.3
Maximum value	1.3×10^{-2}	$\frac{1}{70}$	$\frac{1}{2.7}$	$\frac{1}{1.8}$	$\frac{1}{594}$	2.7

Parameter Set 2

Probability distribution 10% above and below baseline parameter values									
	μ	β	γ	ε	q	τ	α	m	R_0
Baseline value in model	$\frac{1}{4380}$	1.2×10^{-2}	$\frac{1}{77}$	$\frac{1}{3}$	$\frac{1}{2}$	$\frac{1}{653}$	1	$\frac{1}{151}$	2.2
Minimum value	$\frac{1}{4856}$	3.1×10^{-2}	$\frac{1}{85}$	$\frac{1}{3.3}$	$\frac{1}{2.2}$	$\frac{1}{725}$	$\frac{1}{159}$	$\frac{1}{168}$	1.9
1st Quartile	$\frac{1}{4604}$	3.3×10^{-2}	$\frac{1}{81}$	$\frac{1}{3.2}$	$\frac{1}{2.1}$	$\frac{1}{687}$	$\frac{1}{4}$	$\frac{1}{159}$	2.2
Median	$\frac{1}{4380}$	3.5×10^{-2}	$\frac{1}{77}$	$\frac{1}{3}$	$\frac{1}{2}$	$\frac{1}{653}$	$\frac{1}{2}$	$\frac{1}{151}$	2.2
Mean	$\frac{1}{4380}$	3.5×10^{-2}	$\frac{1}{77}$	$\frac{1}{3}$	$\frac{1}{2}$	$\frac{1}{653}$	$\frac{1}{2}$	$\frac{1}{151}$	2.2
3rd Quartile	$\frac{1}{4173}$	3.7×10^{-2}	$\frac{1}{73}$	$\frac{1}{2.9}$	$\frac{1}{1.9}$	$\frac{1}{622}$	$\frac{1}{1.3}$	$\frac{1}{144}$	2.3
Maximum value	$\frac{1}{3982}$	3.8×10^{-2}	$\frac{1}{70}$	$\frac{1}{2.7}$	$\frac{1}{1.8}$	$\frac{1}{594}$	1	$\frac{1}{138}$	2.6

Parameter Set 1

Probability distribution 50% above and below baseline parameter values						
	β	γ	ε	q	τ	R_0
Baseline value in model	1.2×10^{-2}	$\frac{1}{77}$	$\frac{1}{3}$	$\frac{1}{2}$	$\frac{1}{653}$	2.2
Minimum value	6×10^{-3}	$\frac{1}{151}$	$\frac{1}{5}$	$\frac{1}{3.9}$	$\frac{1}{1290}$	0.83
1st Quartile	9×10^{-3}	$\frac{1}{103}$	$\frac{1}{4}$	$\frac{1}{2.6}$	$\frac{1}{863}$	1.7
Median	1.2×10^{-2}	$\frac{1}{77}$	$\frac{1}{3}$	$\frac{1}{2}$	$\frac{1}{654}$	2.2
Mean	1.2×10^{-2}	$\frac{1}{77}$	$\frac{1}{3}$	$\frac{1}{2}$	$\frac{1}{653}$	2.2
3rd Quartile	1.5×10^{-2}	$\frac{1}{62}$	$\frac{1}{2.4}$	$\frac{1}{1.6}$	$\frac{1}{523}$	2.9
Maximum value	1.8×10^{-2}	$\frac{1}{52}$	$\frac{1}{2}$	$\frac{1}{1.3}$	$\frac{1}{432}$	5.1

Parameter Set 2

Probability distribution 50% above and below baseline parameter values									
	μ	β	γ	ε	q	τ	α	m	R_0
Baseline value in model	$\frac{1}{4380}$	3.5×10^{-2}	$\frac{1}{77}$	$\frac{1}{3}$	$\frac{1}{2}$	$\frac{1}{653}$	1	$\frac{1}{151}$	2.2
Minimum value	$\frac{1}{8657}$	1.8×10^{-2}	$\frac{1}{152}$	$\frac{1}{6}$	$\frac{1}{4}$	$\frac{1}{1299}$	$\frac{1}{122}$	$\frac{1}{300}$	0.9
1st Quartile	$\frac{1}{5838}$	2.6×10^{-2}	$\frac{1}{102}$	$\frac{1}{4}$	$\frac{1}{3}$	$\frac{1}{871}$	$\frac{1}{4}$	$\frac{1}{202}$	2
Median	$\frac{1}{4386}$	3.5×10^{-2}	$\frac{1}{77}$	$\frac{1}{3}$	$\frac{1}{2}$	$\frac{1}{652}$	$\frac{1}{2}$	$\frac{1}{151}$	2.2
Mean	$\frac{1}{4382}$	3.5×10^{-2}	$\frac{1}{77}$	$\frac{1}{3}$	$\frac{1}{2}$	$\frac{1}{653}$	$\frac{1}{2}$	$\frac{1}{151}$	2.2
3rd Quartile	$\frac{1}{3521}$	4.3×10^{-2}	$\frac{1}{62}$	$\frac{1}{2.4}$	$\frac{1}{1.6}$	$\frac{1}{524}$	$\frac{1}{1.3}$	$\frac{1}{121}$	2.5
Max	$\frac{1}{2939}$	5.2×10^{-2}	$\frac{1}{51}$	$\frac{1}{2}$	$\frac{1}{1.3}$	$\frac{1}{437}$	1	$\frac{1}{101}$	5.3

Parameter Set 1

Probability distribution 100% above and below baseline parameter values						
	β	γ	ε	q	τ	R_0
Baseline value in model	1.2×10^{-2}	$\frac{1}{77}$	$\frac{1}{3}$	$\frac{1}{2}$	$\frac{1}{653}$	2.2
Minimum value	8.7×10^{-6}	$\frac{1}{7253}$	$\frac{1}{401}$	$\frac{1}{209}$	$\frac{1}{542545}$	0.0026
1st Quartile	6×10^{-3}	$\frac{1}{149}$	$\frac{1}{6}$	$\frac{1}{4}$	$\frac{1}{1307}$	1.2
Median	1.2×10^{-2}	$\frac{1}{76.5}$	$\frac{1}{3}$	$\frac{1}{2}$	$\frac{1}{656}$	2.2
Mean	1.2×10^{-2}	$\frac{1}{77}$	$\frac{1}{3}$	$\frac{1}{2}$	$\frac{1}{653}$	2.2
3rd Quartile	1.8×10^{-2}	$\frac{1}{52}$	$\frac{1}{2}$	$\frac{1}{1.3}$	$\frac{1}{438}$	3.8
Max	2.4×10^{-2}	$\frac{1}{39}$	$\frac{1}{1.5}$	1	$\frac{1}{329}$	142

Parameter Set 2

Probability distribution 100% above and below baseline parameter values									
	μ	β	γ	ε	q	τ	α	m	R_0
Baseline value in model	$\frac{1}{4380}$	3.5×10^{-2}	$\frac{1}{77}$	$\frac{1}{3}$	$\frac{1}{2}$	$\frac{1}{653}$	1	$\frac{1}{151}$	2.2
Minimum value	$\frac{1}{484916}$	5.9×10^{-4}	$\frac{1}{5603}$	$\frac{1}{308}$	$\frac{1}{125}$	$\frac{1}{52096}$	$\frac{1}{189}$	$\frac{1}{9337}$	0.06
1st Quartile	$\frac{1}{8750}$	1.8×10^{-2}	$\frac{1}{152}$	$\frac{1}{6}$	$\frac{1}{4}$	$\frac{1}{1305}$	$\frac{1}{4}$	$\frac{1}{304}$	1.9
Median	$\frac{1}{4373}$	3.5×10^{-2}	$\frac{1}{77}$	$\frac{1}{3}$	$\frac{1}{2}$	$\frac{1}{651}$	$\frac{1}{2}$	$\frac{1}{150}$	2.2
Mean	$\frac{1}{4384}$	3.5×10^{-2}	$\frac{1}{77}$	$\frac{1}{3}$	$\frac{1}{2}$	$\frac{1}{653}$	$\frac{1}{2}$	$\frac{1}{151}$	2.2

3rd Quartile	$\frac{1}{2934}$	5.2x10-2	$\frac{1}{51}$	$\frac{1}{2}$	$\frac{1}{1.3}$	$\frac{1}{436}$	$\frac{1}{1.3}$	$\frac{1}{101}$	2.8
Max	$\frac{1}{2191}$	6.9x10-2	$\frac{1}{39}$	$\frac{1}{1.5}$	1	$\frac{1}{329}$	1	$\frac{1}{76}$	17

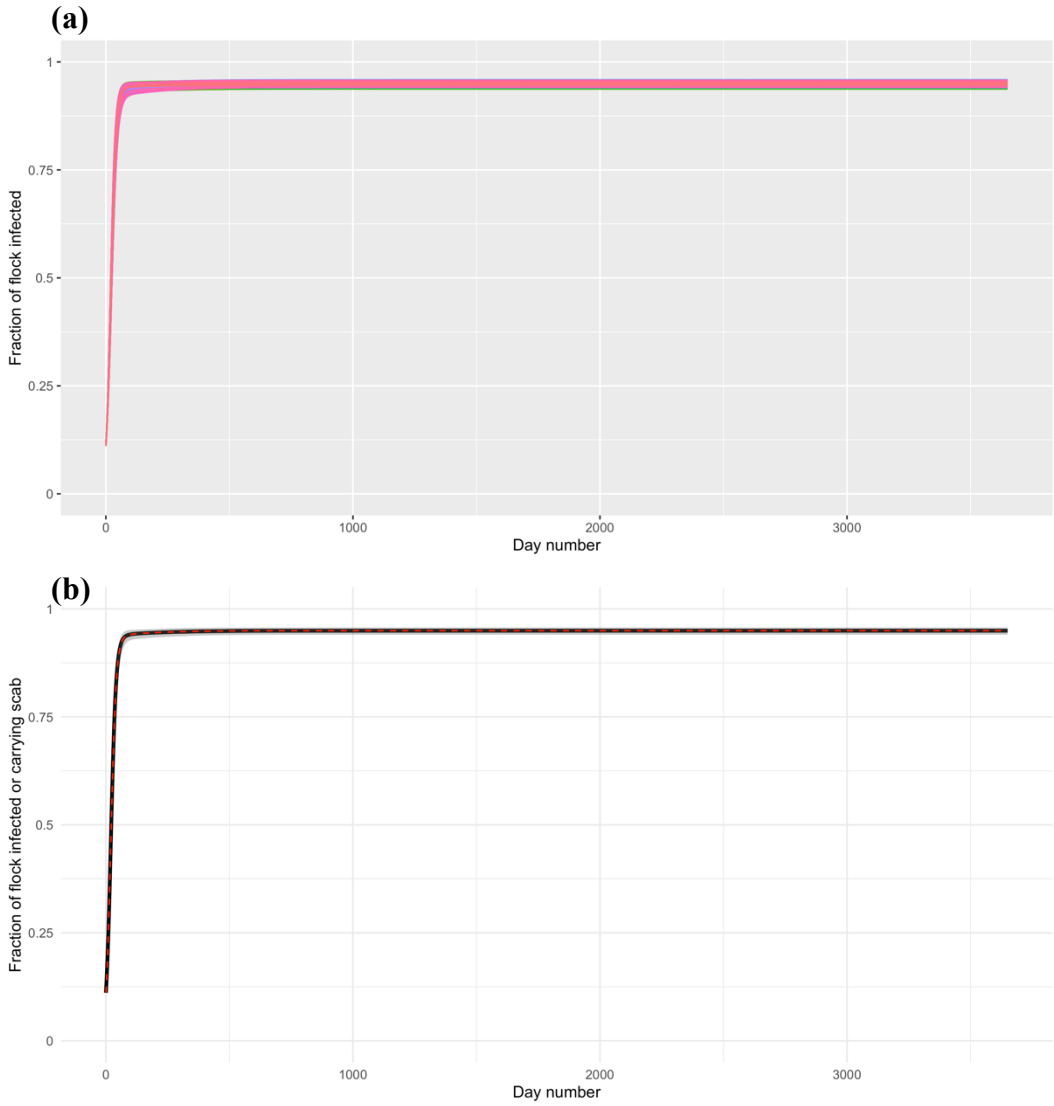


Fig. 4.7. Uncertainty Analysis of the deterministic model, using LHS, with PDF range 10% above and below the baseline parameter values of Parameter Set 1. Parameters that had a baseline value of 0 did not undergo LHS and were kept at their baseline value. At time step one, 1/9 sheep is infected. The PDF distribution was uniform for all parameters. (a) The fraction of flock infected over 3650 time steps (10 years) is are given for 100 parameter combinations (N=100). (b) The results are summarised, showing the median result (black line), interquartile ranges (dark grey shading) and 97.5th and 2.5th percentiles (light grey shading). The red dashed line in (b) indicates the result from the R deterministic run of the model under the baseline parameters specified in section 4.3.5.

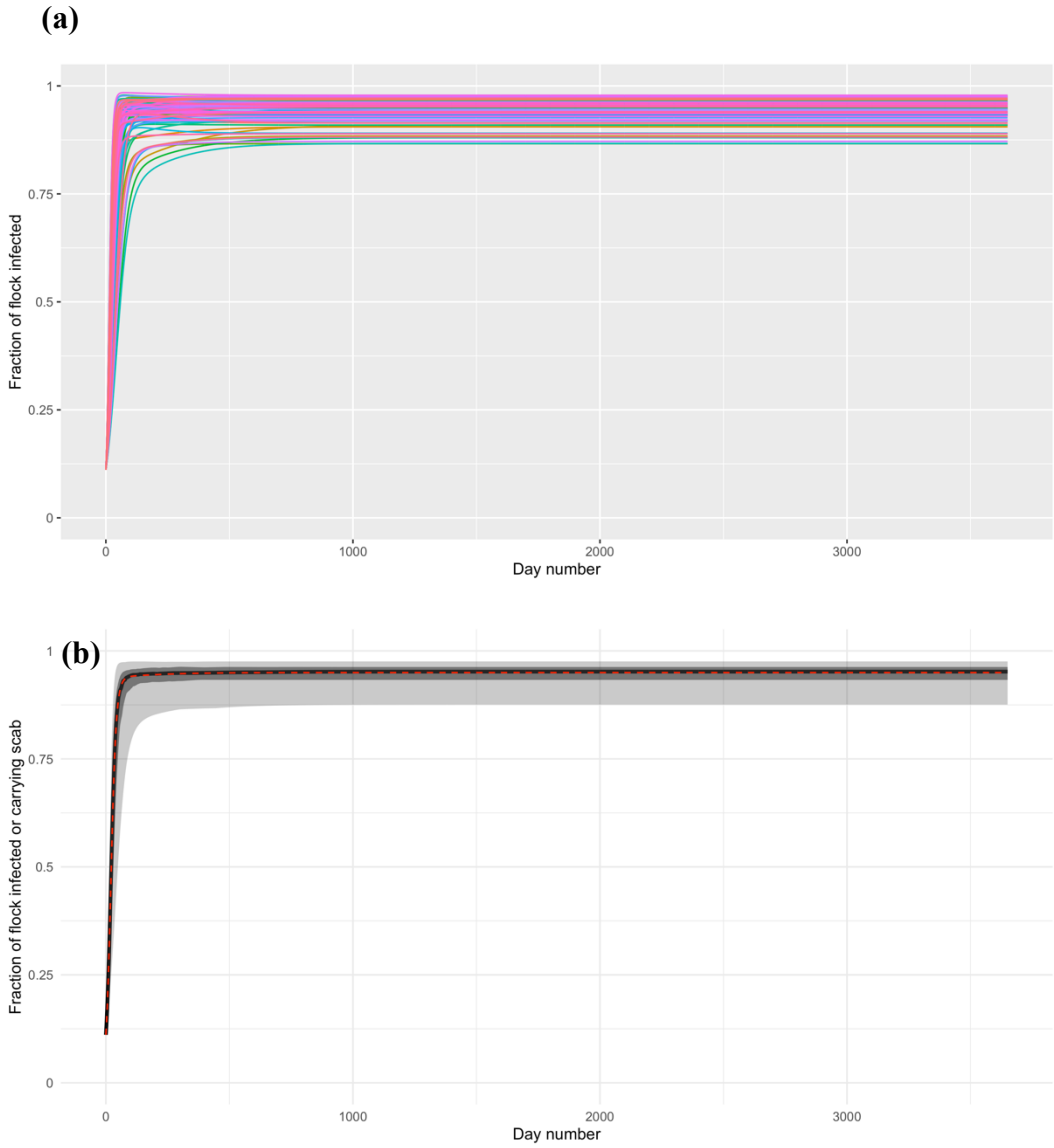


Fig. 4.8. Uncertainty Analysis of the deterministic model, using LHS, with PDF range 50% above and below the baseline parameter values of Parameter Set 1. Parameters that had a baseline value of 0 did not undergo LHS and were kept at their baseline value. At time step one, 1/9 sheep is infected. The PDF distribution was uniform for all parameters. (a) The fraction of flock infected over 3650 time steps (10 years) is are given for 100 parameter combinations (N=100). (b) The results are summarised, showing the median result (black line), interquartile ranges (dark grey shading) and 97.5th and 2.5th percentiles (light grey shading). The red dashed line in (b) indicates the result from the R deterministic run of the model under the baseline parameters specified in section 4.3.5.

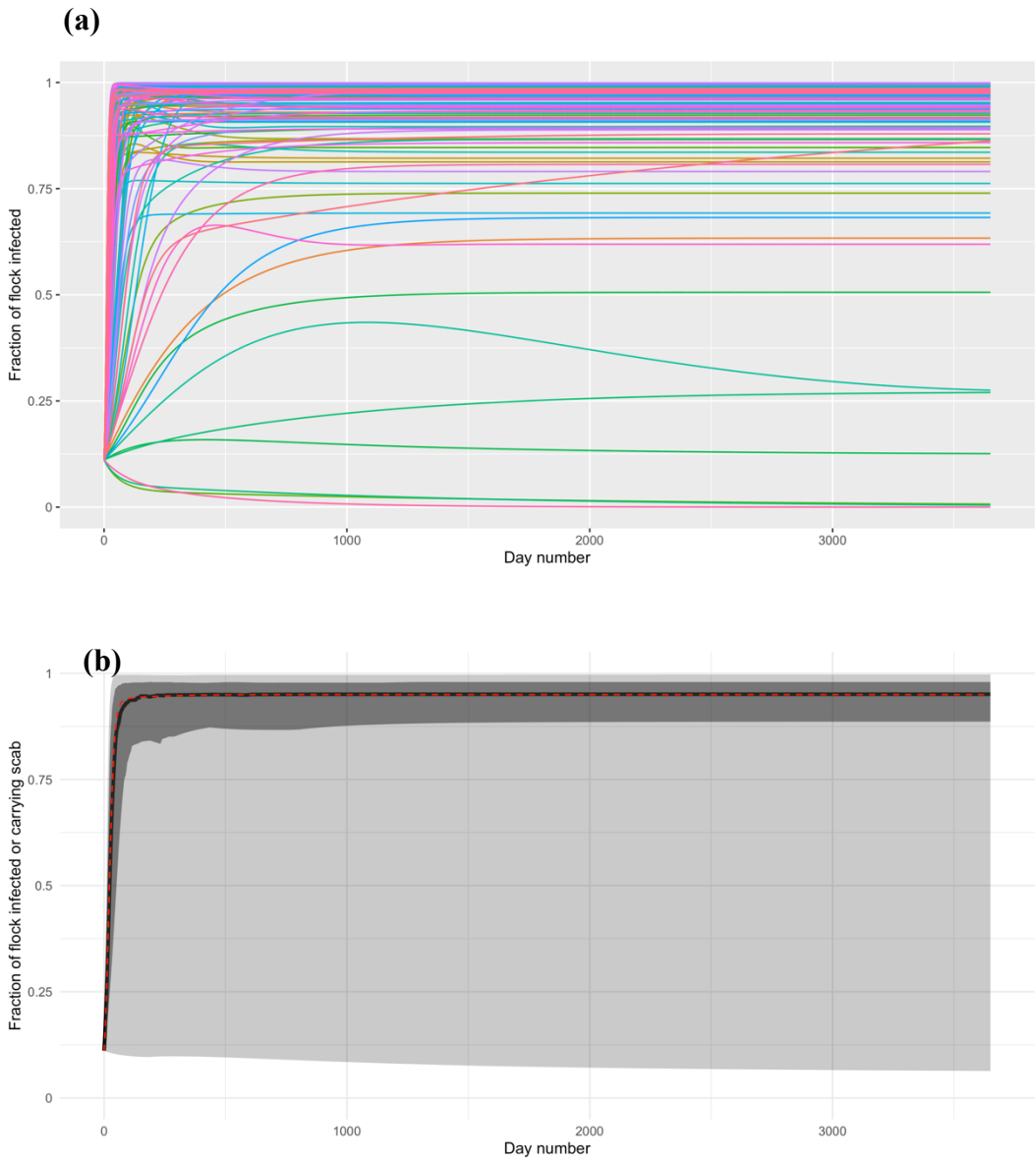


Fig. 4.9. Uncertainty Analysis of the deterministic model, using LHS, with PDF range 100% above and below the baseline parameter values of Parameter Set 1. Parameters that had a baseline value of 0 did not undergo LHS and were kept at their baseline value. At time step one, 1/9 sheep is infected. The PDF distribution was uniform for all parameters. **(a)** The fraction of flock infected over 3650 time steps (10 years) is are given for 100 parameter combinations (N=100). **(b)** The results are summarised, showing the median result (black line), interquartile ranges (dark grey shading) and 97.5th and 2.5th percentiles (light grey shading). The red dashed line in (b) indicates the result from the R deterministic run of the model under the baseline parameters specified in section 4.3.5.

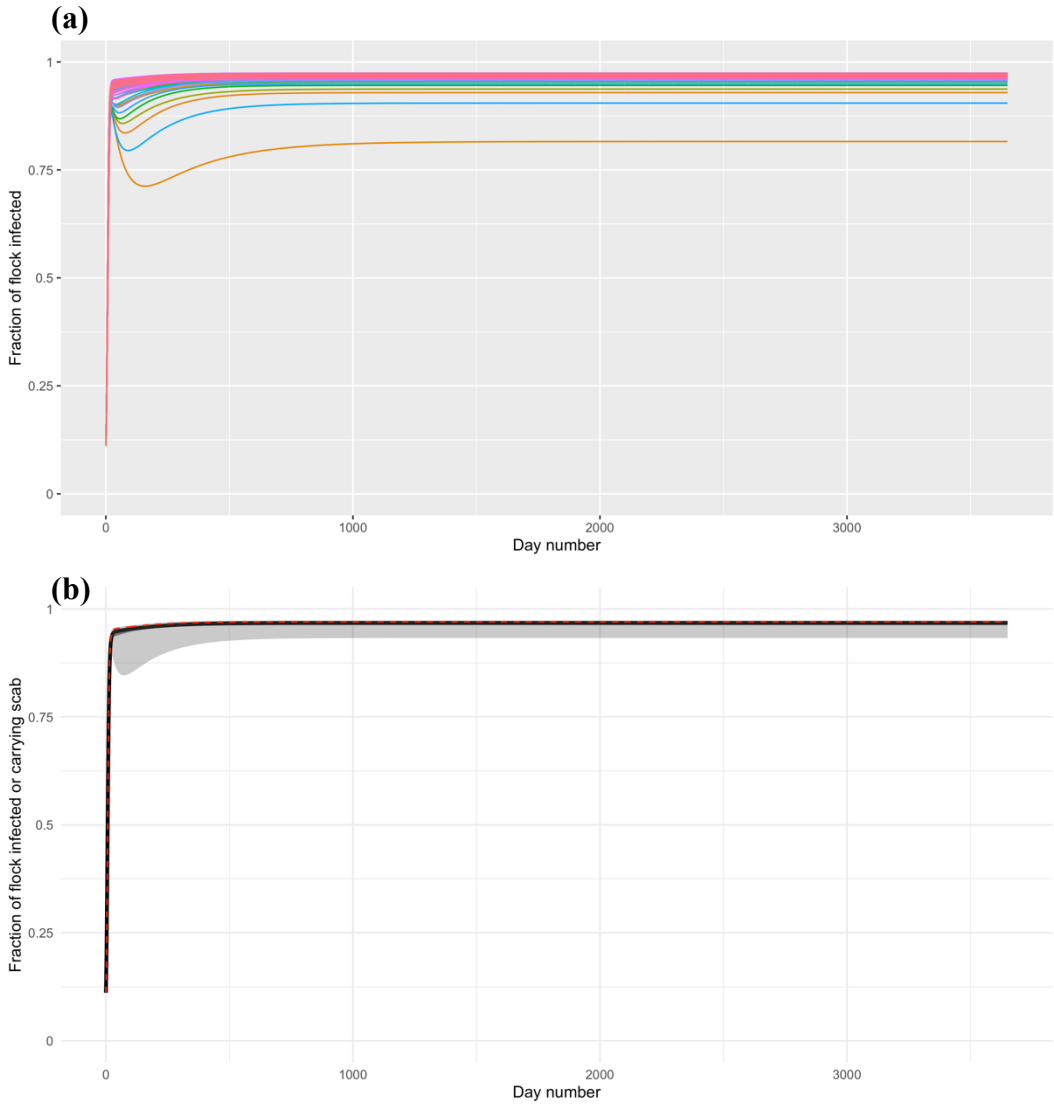


Fig. 4.10. Uncertainty Analysis of the deterministic model, using LHS, with PDF range 10% above and below the baseline parameter values of Parameter Set 2 (excluding the restocking rate, α, which had a PDF range of 0-1). Parameters that had a baseline value of 0 did not undergo LHS and were kept at their baseline value. At time step one, 1/9 sheep is infected. The PDF distribution was uniform for all parameters. (a) The fraction of flock infected over 3650 time steps (10 years) is are given for 100 parameter combinations (N=100). (b) The results are summarised, showing the median result (black line), interquartile ranges (dark grey shading) and 97.5th and 2.5th percentiles (light grey shading). The red dashed line in (b) indicates the result from the R deterministic run of the model under the baseline parameters specified in section 4.3.5.

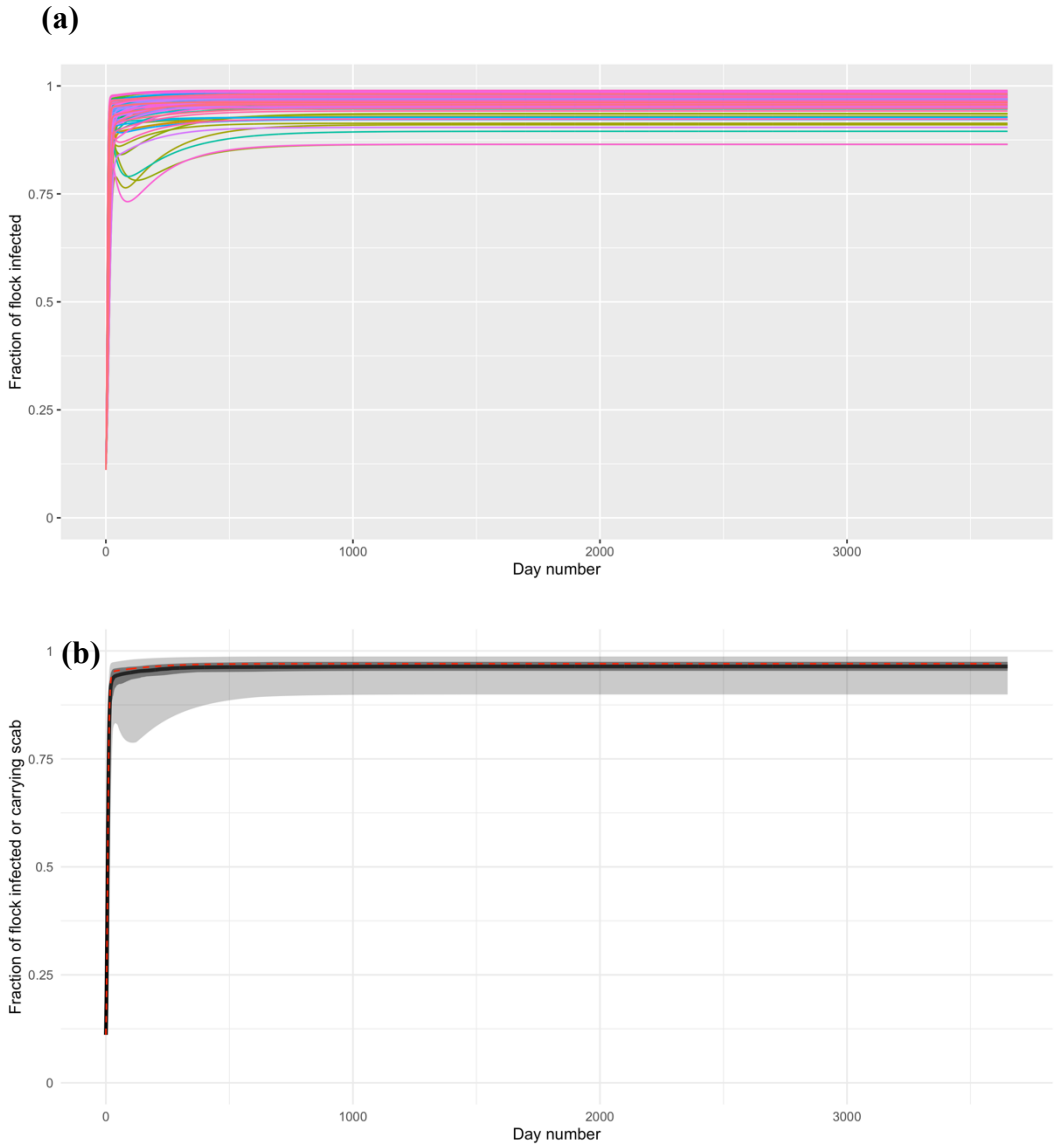


Fig. 4.11. Uncertainty Analysis of the deterministic model, using LHS, with PDF range 50% above and below the baseline parameter values of Parameter Set 2 (excluding the restocking rate, α, which had a PDF range of 0-1). Parameters that had a baseline value of 0 did not undergo LHS and were kept at their baseline value. At time step one, 1/9 sheep is infected. The PDF distribution was uniform for all parameters. (a) The fraction of flock infected over 3650 time steps (10 years) is are given for 100 parameter combinations (N=100). (b) The results are summarised, showing the median result (black line), interquartile ranges (dark grey shading) and 97.5th and 2.5th percentiles (light grey shading). The red dashed line in (b) indicates the result from the R deterministic run of the model under the baseline parameters specified in section 4.3.5.

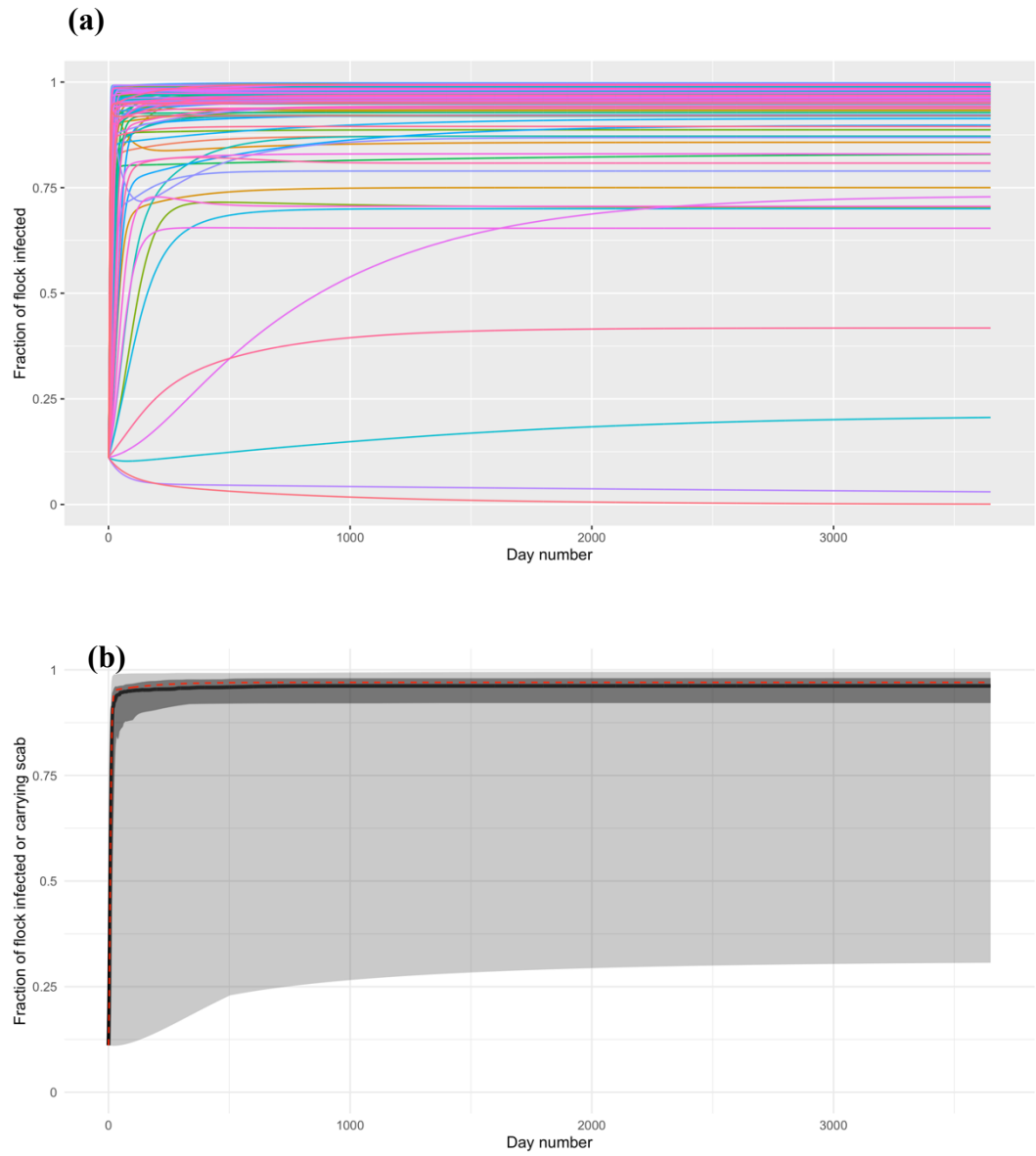
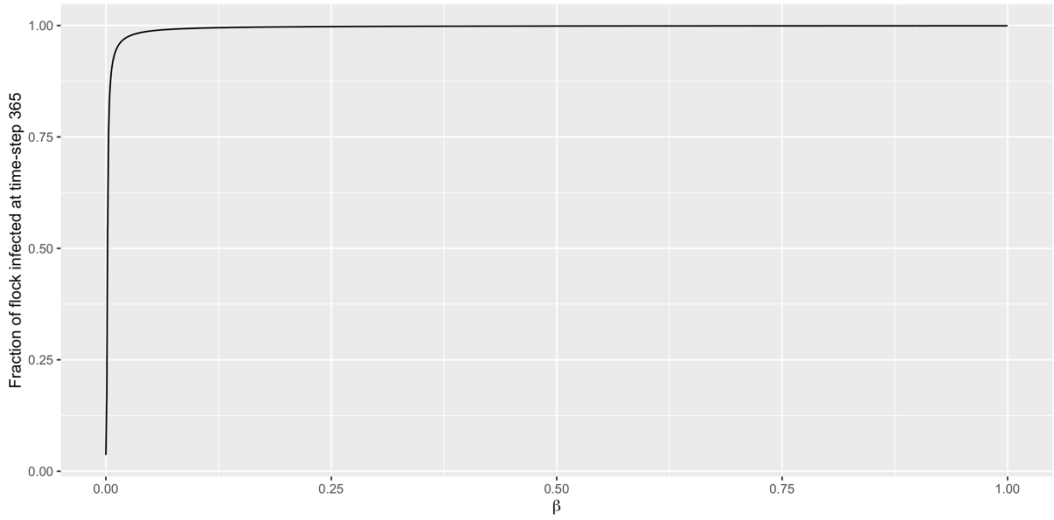


Fig. 4.12. Uncertainty Analysis of the deterministic model, using LHS, with PDF range 100% above and below the baseline parameter values of Parameter Set 2 (excluding the restocking rate, α, which had a PDF range of 0-1). Parameters that had a baseline value of 0 did not undergo LHS and were kept at their baseline value. At time step one, 1/9 sheep is infected. The PDF distribution was uniform for all parameters. (a) The fraction of flock infected over 3650 time steps (10 years) is are given for 100 parameter combinations (N=100). (b) The results are summarised, showing the median result (black line), interquartile ranges (dark grey shading) and 97.5th and 2.5th percentiles (light grey shading). The red dashed line in (b) indicates the result from the R deterministic run of the model under the baseline parameters specified in section 4.3.5.

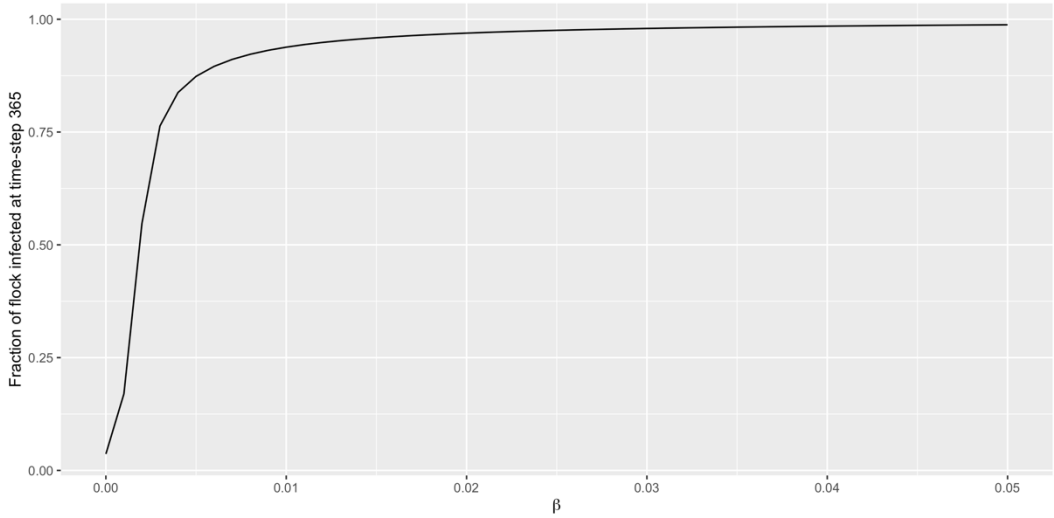
4.4.3.2 One-at-a-time sensitivity analyses

The relationship between each parameter and the model output is non-linear and monotonic (Fig. 4.13) for most parameters, which means that a PRCC can be used on the LHS results to measure the importance of each of these parameters to the model output (Fig. 4.14). The exception to this is γ from Parameter Set 2, which did not appear to have a completely monotonic relationship with the model output (Fig. 4.13qrs). As well as a PRCC, a Kruskal-Wallis rank sum test was also used for this parameter as described in section 4.3.6.3.

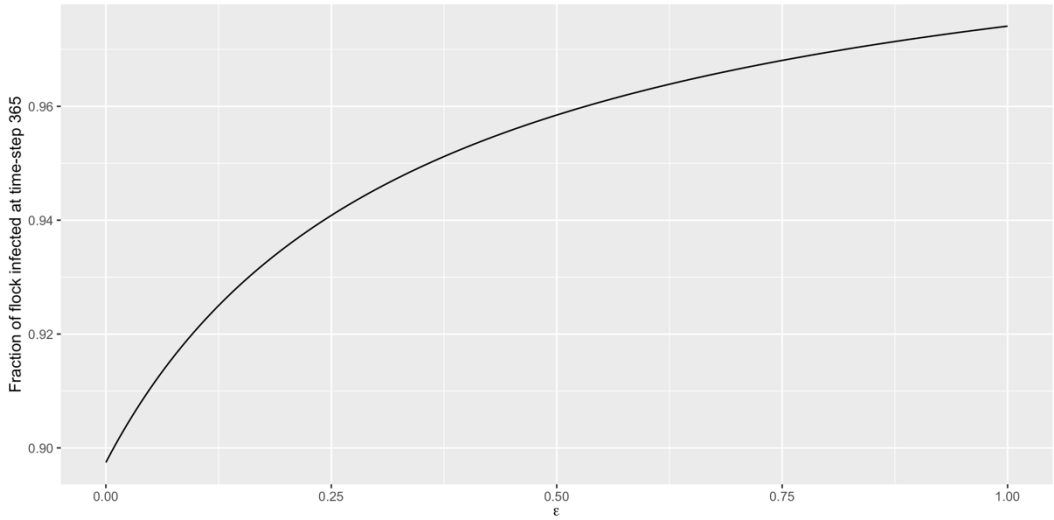
a


Fraction of flock infected at time-step 365
1.00
0.75
0.50
0.25
0.00
0.00
0.25
0.50
0.75
1.00
β

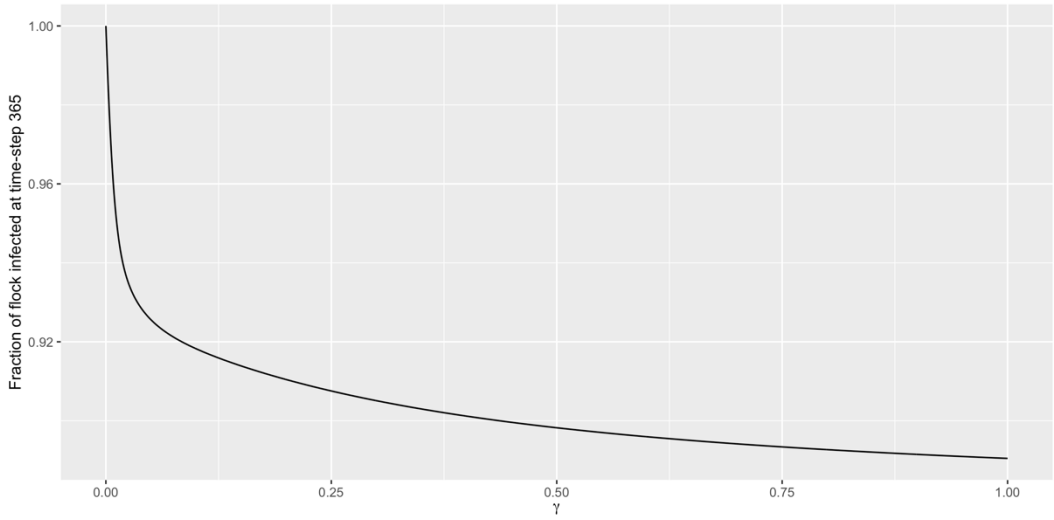
b


Fraction of flock infected at time-step 365
1.00
0.75
0.50
0.25
0.00
0.00
0.01
0.02
0.03
0.04
0.05
β

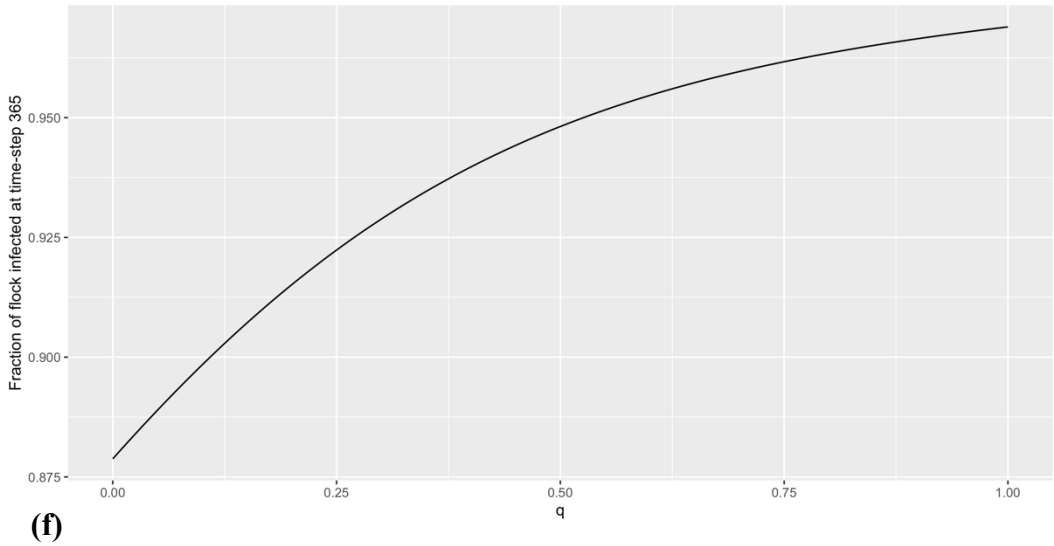
(c)


Fraction of flock infected at time-step 365
0.96
0.94
0.92
0.90
0.00
0.25
0.50
0.75
1.00
ε

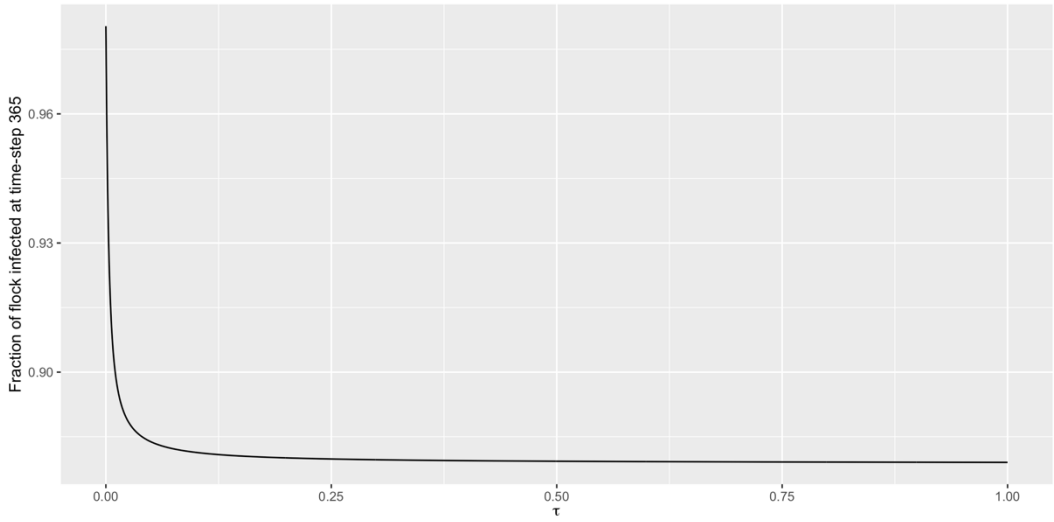
(d)


Fraction of flock infected at time-step 365
1.00
0.96
0.92
0.00
0.25
0.50
0.75
1.00
γ

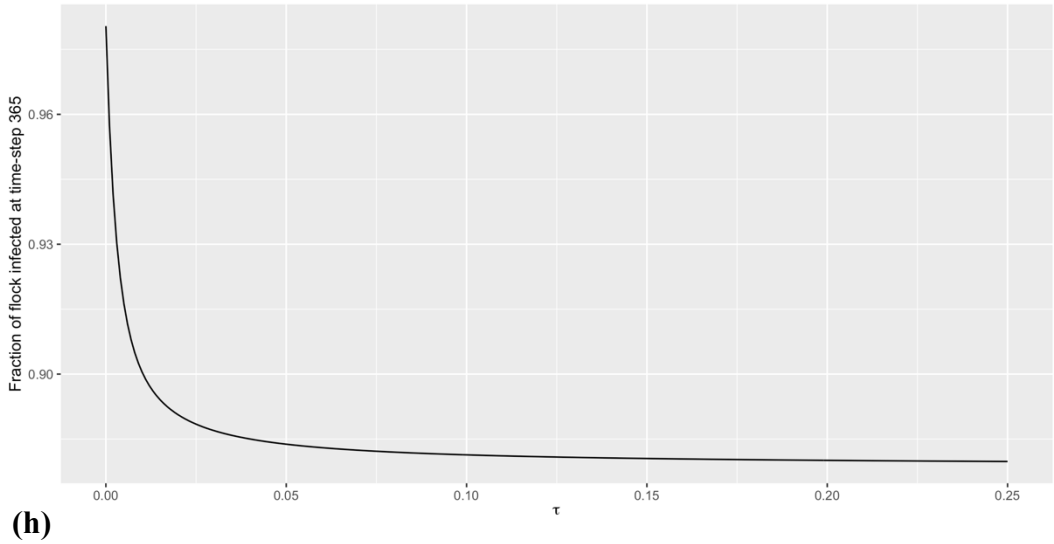
(e)


Fraction of flock infected at time-step 365
0.950
0.925
0.900
0.875
0.00
0.25
0.50
0.75
1.00
q

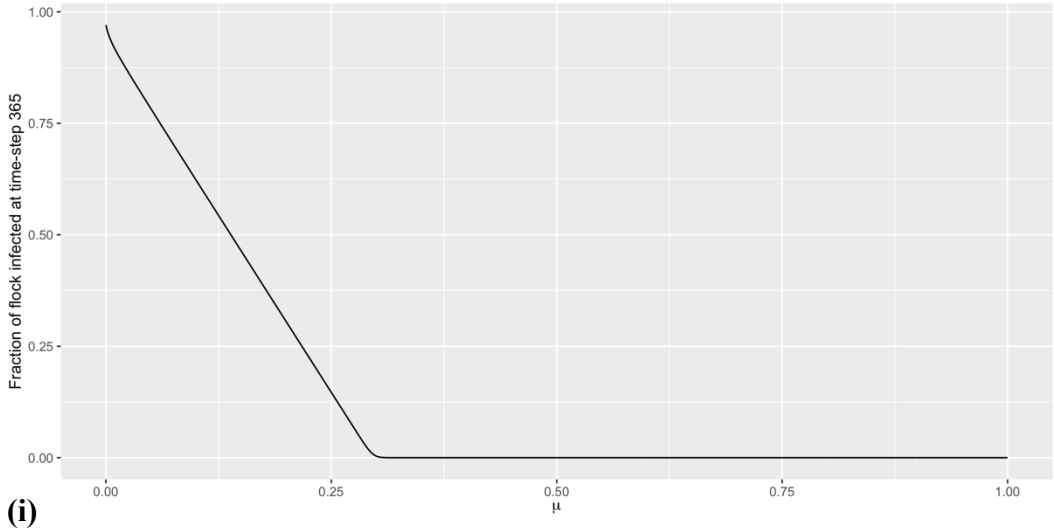
(f)


Fraction of flock infected at time-step 365
0.96
0.93
0.90
0.00
0.25
0.50
0.75
1.00
τ

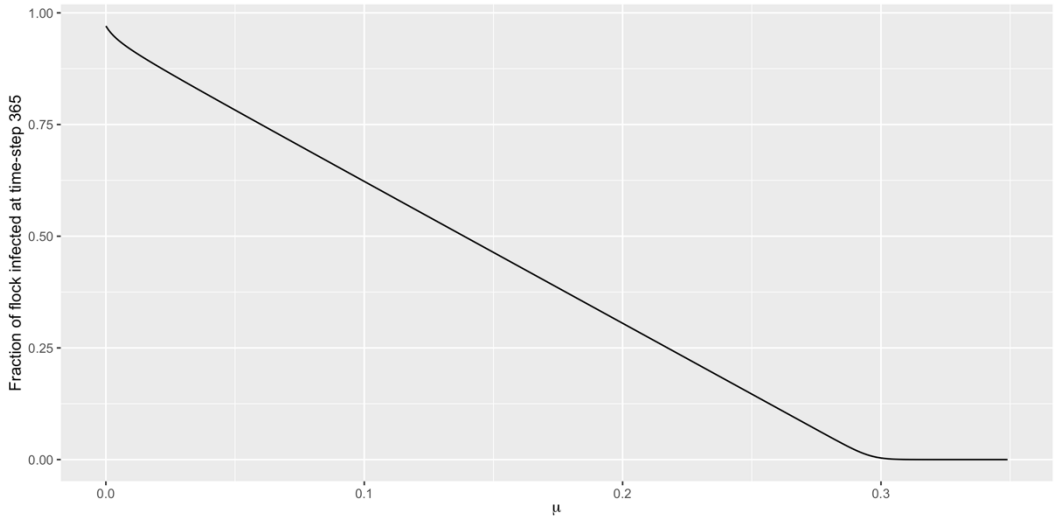
(g)


Fraction of flock infected at time-step 365
0.96
0.93
0.90
0.00
0.05
0.10
0.15
0.20
0.25
τ

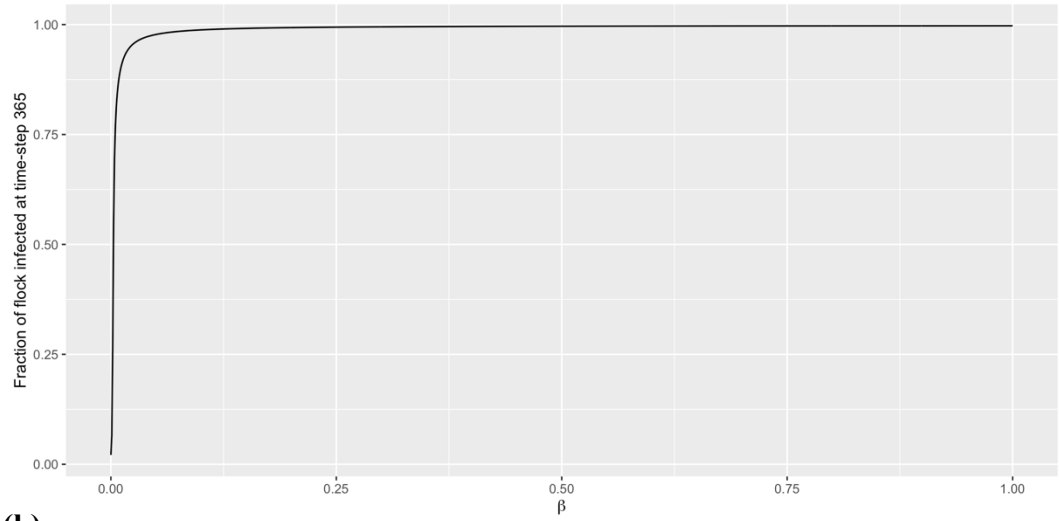
(h)


Fraction of flock infected at time-step 365
1.00
0.75
0.50
0.25
0.00
0.00
0.25
0.50
0.75
1.00
μ

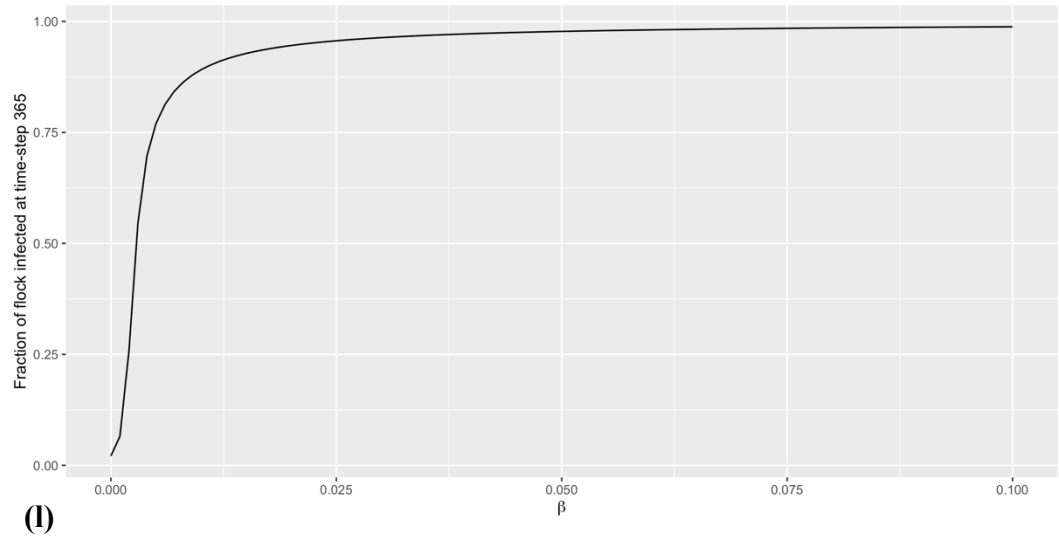
(i)


Fraction of flock infected at time-step 365
1.00
0.75
0.50
0.25
0.00
0.0
0.1
0.2
0.3
μ

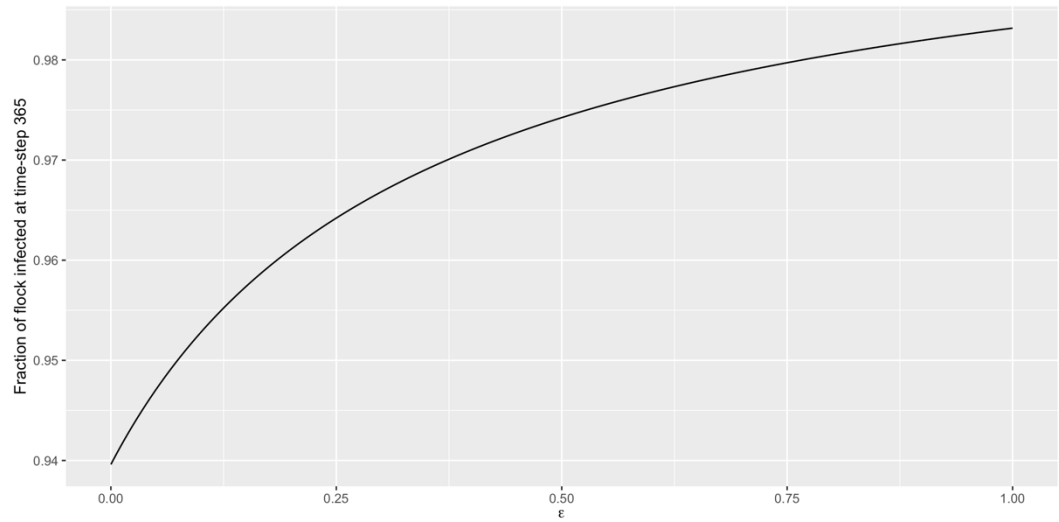
(j)


Fraction of flock infected at time-step 365
1.00
0.75
0.50
0.25
0.00
0.00
0.25
0.50
0.75
1.00
β

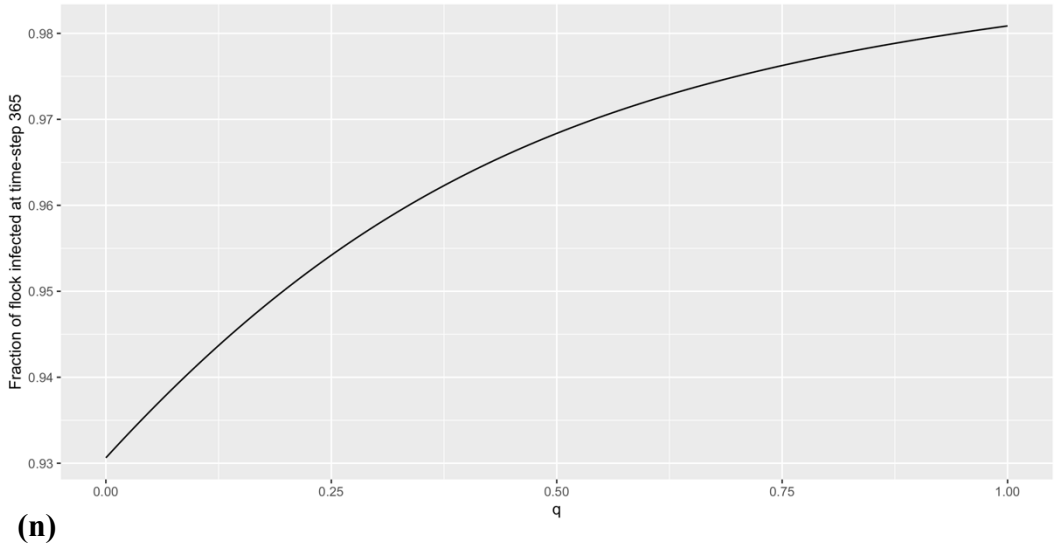
(k)


Fraction of flock infected at time-step 365
1.00
0.75
0.50
0.25
0.00
0.000
0.025
0.050
0.075
0.100
β

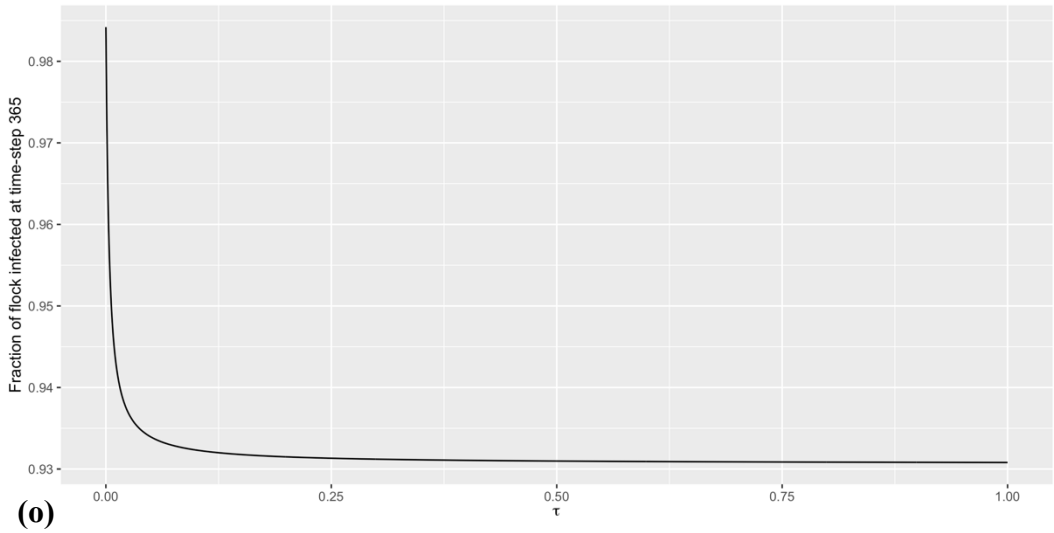
(l)


Fraction of flock infected at time-step 365
0.98
0.97
0.96
0.95
0.94
0.00
0.25
0.50
0.75
1.00
ε

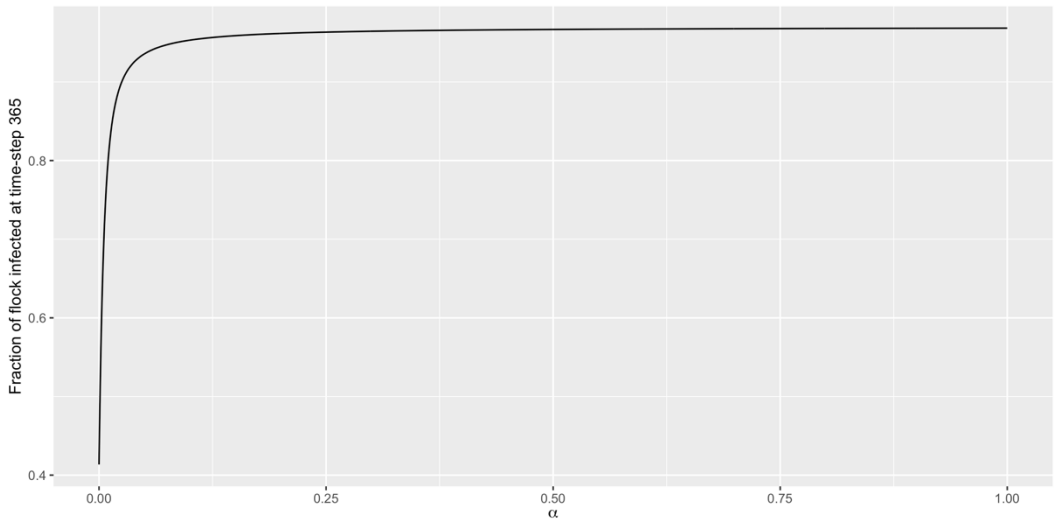
(m)


Fraction of flock infected at time-step 365
0.98
0.97
0.96
0.95
0.94
0.93
0.00
0.25
0.50
0.75
1.00
q

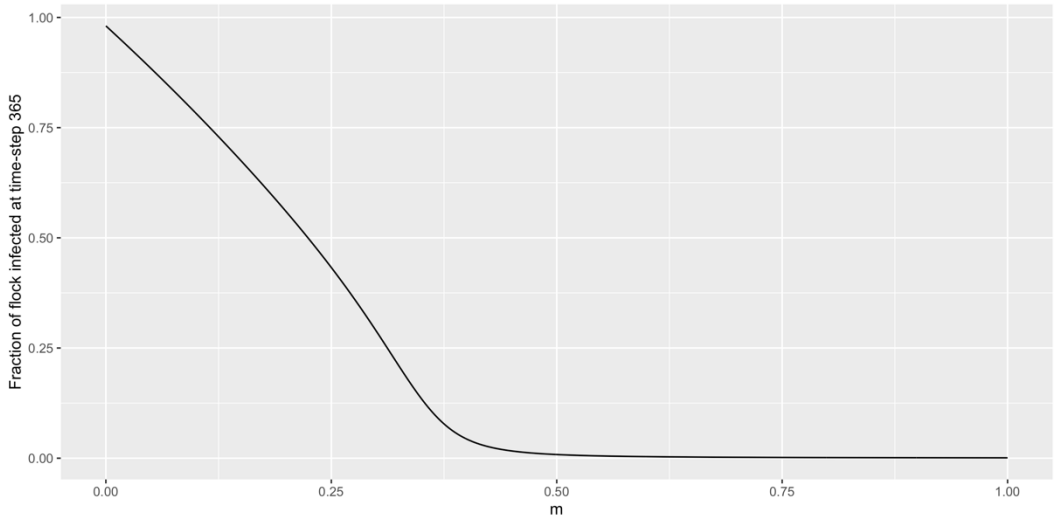
(n)


Fraction of flock infected at time-step 365
0.98
0.97
0.96
0.95
0.94
0.93
0.00
0.25
0.50
0.75
1.00
τ

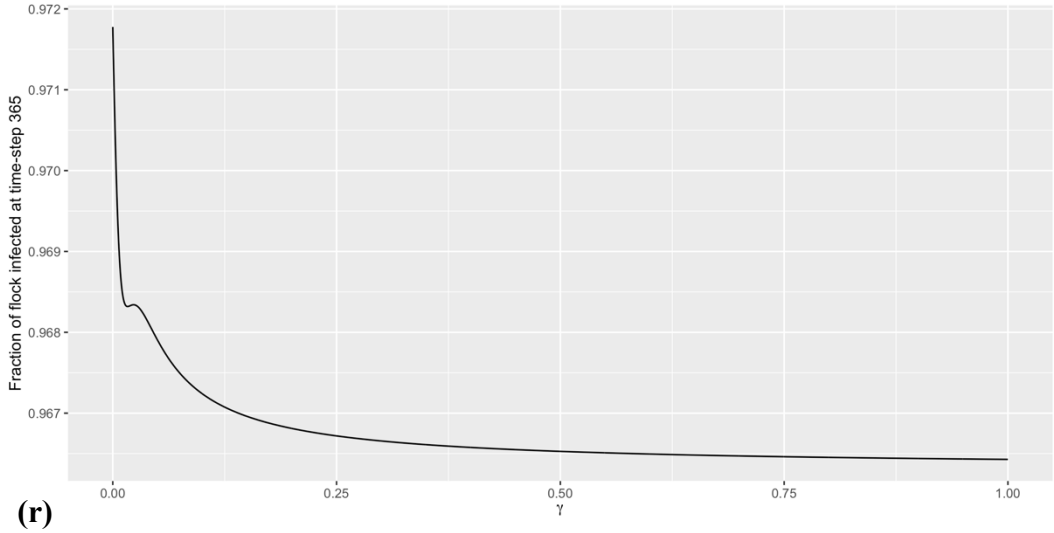
(o)


Fraction of flock infected at time-step 365
0.8
0.6
0.4
0.00
0.25
0.50
0.75
1.00
α

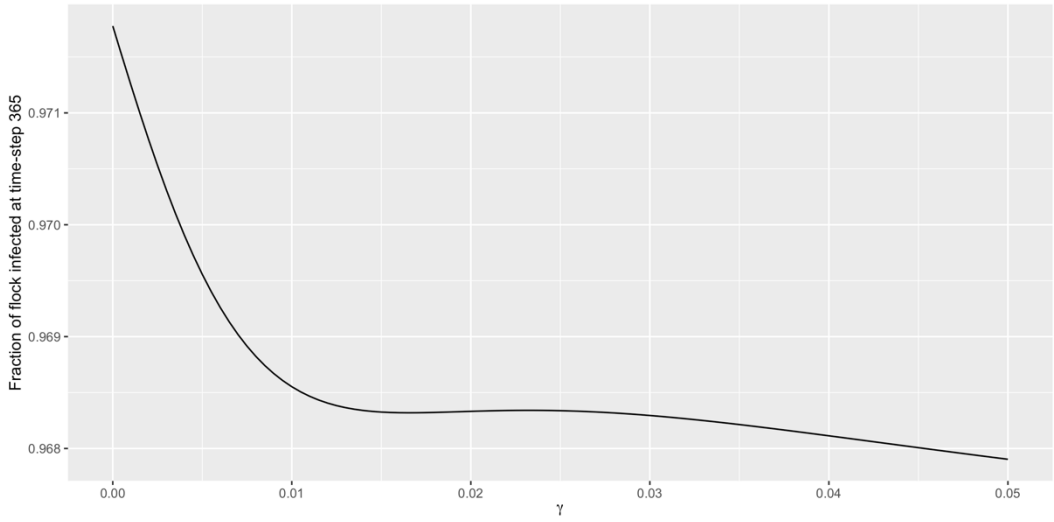
(p)


Fraction of flock infected at time-step 365
1.00
0.75
0.50
0.25
0.00
0.00
0.25
0.50
0.75
1.00
m

(q)


Fraction of flock infected at time-step 365
0.972
0.971
0.970
0.969
0.968
0.967
0.00
0.25
0.50
0.75
1.00
γ

(r)


Fraction of flock infected at time-step 365
0.971
0.970
0.969
0.968
0.00
0.01
0.02
0.03
0.04
0.05
γ

(s)

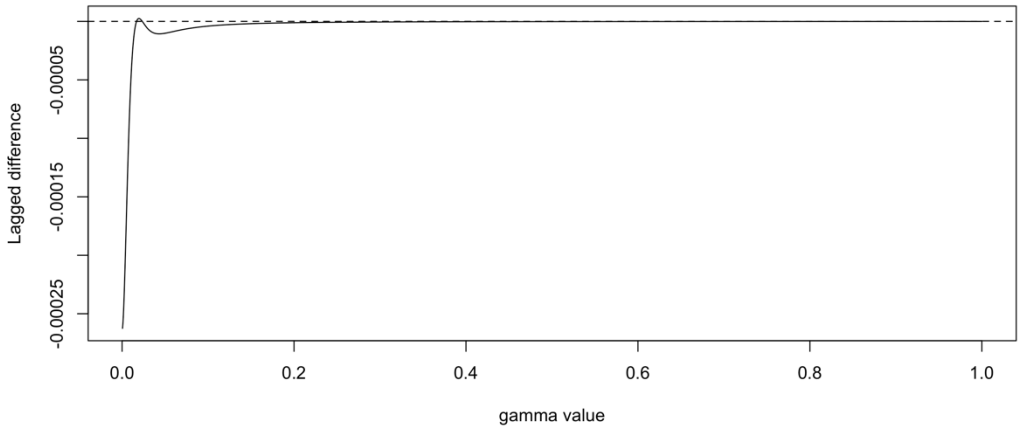


Fig. 4.13. Relationship between parameters and the model output when all other parameters are kept at a baseline level and the parameter of interest is varied from 0 to 1 by 0.001. This was done for the baseline values of Parameter Set 1 (a-g) and Parameter Set 2 (h-s). S is a lagged difference graph to investigate whether the recovery rate is monotonic or not (if it is above 0 then it is going a different direction and is not monotonic). The model output given is the fraction of the flock that are infected or carriers at time step 3650 when 1 sheep was infected with sheep scab at time step 0 and 8 sheep were susceptible. These results are from the deterministic version of the within-farm SICTD model of sheep scab.

4.4.3.3 *Partial rank correlation coefficient and Kruskal-Wallis rank sum test*

A PRCC value greater than 0.5 in magnitude indicates that the output is sensitive to the input and it is considered to be significant if the *p*-value is less than 0.05 (Pennington, 2015). For Parameter Set 1, there is a strong, significant, positive correlation between the transmission rate (β) and the model output, as well as between the reduced transmission rate for carriers (ε) and the model output. There is a strong, significant, negative correlation between the recovery rate (γ) and the model output (Fig 4.15a). For Parameter Set 2, there is a strong, significant, positive correlation between the transmission rate (β) and the model output, as well as a significant positive correlation between the proportion of infecteds that become carriers (*q*) and the model output (Fig 4.15b). All other parameters from both parameter sets had a PRCC value below 0.5 and so the model is not considered to be strongly sensitive to these parameters, however, the sensitivity that exists is significant (Fig 4.15).

The correlation between the model output and the recovery rate (γ) was not significant in the PRCC for Parameter Set 2. As this parameter appeared to not be completely monotonic (Fig 4.13ars), a Kruskal-Wallis rank sum test was performed with two groups and then again with ten groups on the inputs for the recovery rate and the model outputs in the LHS for both parameter sets. The relationship between the recovery rate inputs and the model output when using the other LHS values for Parameter Set 1 suggested that there was a non-monotonic relationship between the recovery rate and the model output when the values for recovery rate were split into ten groups (χ^2 = 22.88, p <0.05) and when they were split into 2 (χ^2 = 8.0, p <0.05). However, there was no significant difference between the groups when using Parameter Set 2 with the values for the recovery rate split into ten groups (χ^2 = 13.5, p >0.05) and two groups (χ^2 = 0.27, p >0.05). Box plots showing the groups of recovery rate values used and the model outputs are given in the Appendix.

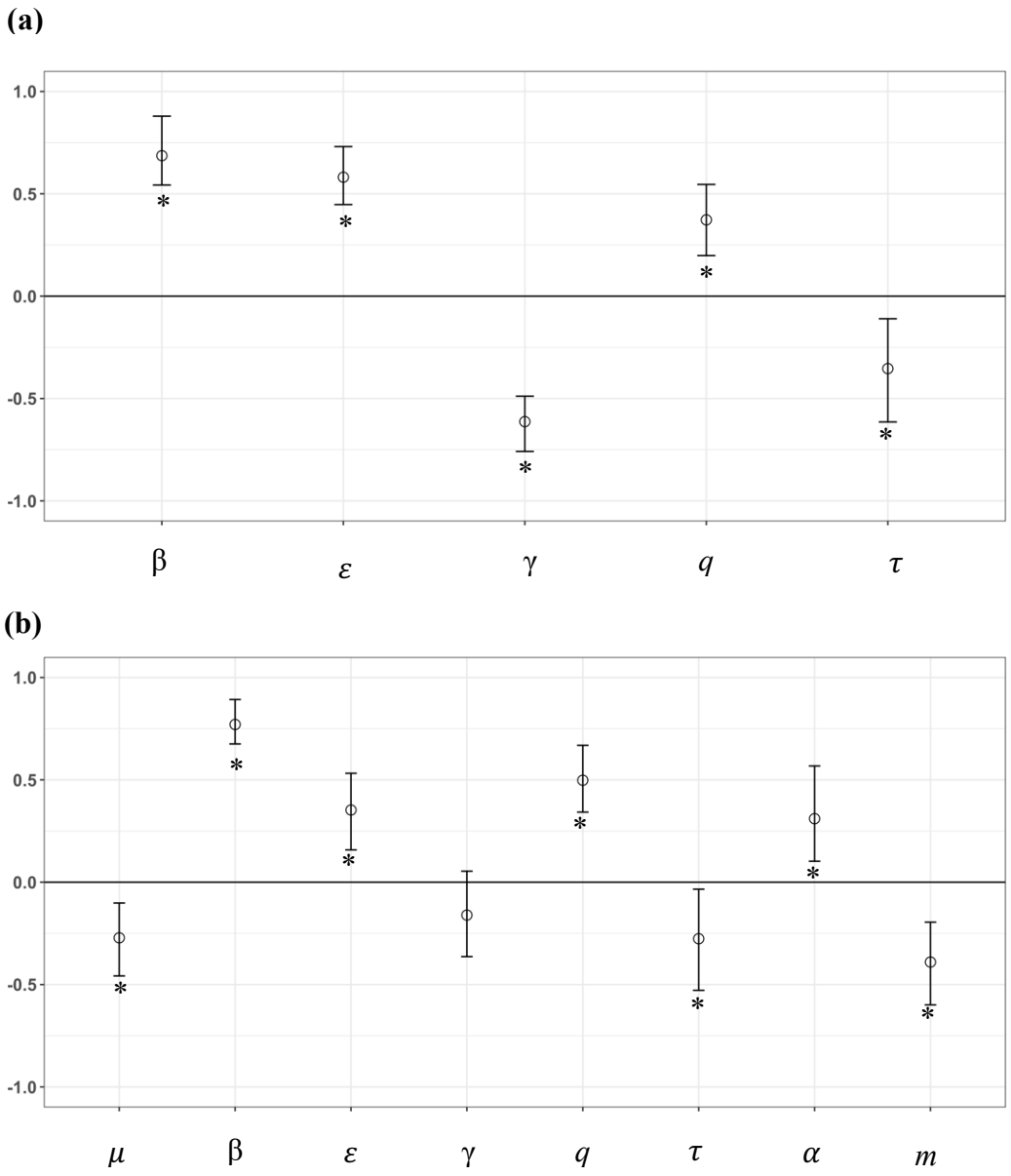


Fig 4.14. Partial rank correlation coefficient on Latin Hypercube sampling for **(a)** Parameter Set 1: transmission rate (β), recovery rate (γ), transmission scaling rate for carriers (ε), proportion of acute infections that become carriers (q), and the rate at which carriers recover (τ) **(b)** Parameter Set 2: includes the same parameters as (a), as well as the rate of natural births and deaths (μ), the restocking rate (α) and the mortality rate (m). This was for the deterministic version of the within-farm SICTD model for sheep scab, where the results from the LHS with PDF range 100% above and below the baseline value. The output observed was the number of sheep infected (acute infections plus carriers) at time step 3650. A star indicates that the p value for the PRCC was less than 0.05 for the test statistic of the significance that the partial rank correlation coefficient is greater than or less than zero. The error bars indicate the confidence level of the bootstrap confidence intervals when there are 1000 replicates and the confidence level of the bootstrap confidence intervals is 0.95.

4.5 DISCUSSION

The within-farm model described in this chapter has been expanded from the within-farm model in Chapter 2 to include a carrier compartment and the parameterisation of the model has been explored further.

4.5.1 Initial results from the model and from the model testing

Overall, the results from both the stochastic and deterministic versions of the model were thought to be from the same distribution as the Berriatua et al. (1999) experimental data, when the parameters match the conditions in the experiments (Fig. 4.3a, Fig. 4.4a). These results give confidence in the model structure (now that a carrier compartment has been added) and in these parameters when modelling the transmission of sheep scab in this setting.

However, it is unlikely that Parameter Set 1 would accurately capture the scab transmission dynamics in all the sheep holding settings in Great Britain, since the flock numbers were much lower than seen for an average sheep flock (Table 3.3, Chapter 3) and area in the model is assumed to be constant between flocks. As the model is density dependent, larger flock sizes have much higher rates of transmission in the model than would be seen if the area of a holding was included. In the current chapter a simulation is run with 200 sheep rather than with 9 (the average flock size in the experiments) resulting in the epidemic peak being reached sooner and the endemic equilibrium being reached later. Although the rate of transmission is expected to be greater in a large flock where individuals have more contacts, it was not possible to test whether the result for a 200 sheep flock was accurate due to a lack of experimental data on larger flock sizes. It could be an overestimate since the area of a holding is unlikely to be constant between a flock of 9 sheep and a flock of 200 sheep. Future improvements to the model could be to include stocking density and comparing the model output to experimental results, if data becomes available on the dynamics of sheep scab transmission in larger flocks.

Since the Berriatua experiments only occurred over a period of fourteen weeks, Parameter Set 1 does not allow for disease mortalities, natural births and deaths and restocking, all of which are events that may occur over a longer time period (Berriatua et al., 1999). Parameter Set 2 contained estimates from the literature of parameters for these events. The model output when using Parameter Set 2 was

found to be from a different distribution when compared to the experimental results from Berriatua et al. (1999). The deterministic result did not lie within the 2.5th and 97.5th percentiles of the experimental results and consistently overestimated the rate at which sheep became infected in comparison to the experimental results (Fig. 4.4a), which could be explained by the higher transmission rate. In addition, this could be because including natural births and deaths, as well as disease mortality and restocking results in more new susceptibles throughout the simulation which can affect disease dynamics (Keeling & Rohani, 2008), often allowing the new epidemics to occur when the disease would otherwise have died out. However, a second epidemic did not occur here which may have been because the new susceptibles were introduced gradually over time. This could suggest that Parameter Set 2 as used in this chapter impacts the short term dynamics, but not the long term dynamics and therefore would not be useful in simulations over a longer time period. However, it is not possible to confirm whether Parameter Set 2 is not a realistic set of values to use for long term dynamics since there is no experimental data that matches these conditions. If other data become available on the dynamics of sheep scab over a longer period of time than in the Berriatua study, this may lead to further improvements in the accuracy of the model.

4.5.2 Insights from the uncertainty and sensitivity analyses

The results from all iterations of the LHS match the positive correlation between time and the fraction of flock infected seen in the model results (Fig. 4.7- 12) and runs to endemic equilibrium. However, as the PDF ranges increase for each iteration of the LHS, so do the confidence intervals, which is to be expected. The final size at endemic equilibrium is impacted by the variation in the parameter values, however, at the range of values used in the uncertainty analysis here, endemic equilibrium is always reached within the 10 year period. As the PDF distribution was uniform, it is expected that the variability in the output seen here is more extreme than if a different distribution had been used. In addition, as the correlations between the parameters were not included, this may have also increased the variability in the results.

The OAT analyses (Fig. 4.13) and the PRCC () both demonstrated that β has the strongest positive relationship with the model output when using both Parameter Sets as baseline values for the LHS. The PRCC indicated that this relationship is

strong and significant and that β is the most sensitive parameter. Other parameters that were sensitive included the reduced transmission rate for carriers (ε) and the recovery rate (γ) (with Parameter Set 1 as baseline values for LHS) and the proportion of infecteds that become carriers (q) (with Parameter Set 2 as baseline values). Interventions that help to reduce β (transmission rate) may therefore be most important when trying to control sheep scab. As the model is density dependent, then reducing stocking density is likely to help reduce the transmission rate. Quarantining infected sheep will also help to reduce R_0 and henceforth β. None of the parameters included in Parameter Set 2, but not in Parameter Set 1 were sensitive to the model output and so these might not be important to include in the model in the future. However, a different result may have been seen over a time period longer than ten years.

The recovery rate (γ), was the only parameter which may not have a monotonic relationship with the model output. Generally, there was a negative correlation between gamma and the model output, however, when gamma is between the value of 0.015 and 0.025 (and all other values are from Parameter Set 2), there appears to be a positive correlation between gamma and the model output. This may explain why in the PRCC, the recovery rate was not significant for Parameter Set 2. However, the Kruskal-Wallis test also suggests that there might be non-monotonicity when the other values from Parameter Set 1 are used. Since the number of intervals used in this test do have a large impact on test results (Chalom, 2015) although two different ranges of intervals were used, the result may also have suggested non-monotonicity when a different range of intervals is used for Parameter Set 2, as seen in Fig. 4.13.

The protection rate and protection loss rate were not included in any of the UA and SA. This is mainly because they are different to other parameters as they change at different points during a simulation depending on when treatment is used. Future work could perform UA and SA solely on these two parameters to investigate when it might be most effective to use treatment and what proportion of the flock should be treated.

4.5.3 Limitations of the model and model testing

Here, sheep could have two levels of infectiousness in the infected and carrier states, however, the infectiousness of infected sheep is likely to be more variable than this. In order to incorporate this in future, a study which developed a Leslie-matrix model for the life-cycle and population growth of *P. ovis* on a single sheep (Wall et al., 1999) could perhaps be incorporated into a within-farm transmission model of sheep scab, assuming that the risk of transmission from an index case increases with the *P.ovis* population size on the host. Explicitly including the on-host life-cycle and population size of *P.ovis* might help to improve accuracy in future models, however, would make the model more complicated which might be an issue when expanding it to look at between farm transmission as done in Chapter 3.

As discussed in Chapter 2 (section 2.5.2.3), the final size for the Berriatua experiment may be an underestimate and if the experiment had continued longer then 100% of sheep in the flock may have become infected. However, when endemic equilibrium is reached, 100% of the flock are infected or carriers in the deterministic model, regardless of flock size (9 or 200 sheep) and regardless of the parameter set used (Table 4.4). Therefore, the possible underestimation of the final size for the Berriatua experiment may not affect the model output too strongly, although it may take longer for endemic equilibrium to be reached in the model than seen in reality.

It is clear that more data on within-farm transmission of sheep scab would be welcome in improving the accuracy of the model. In addition, the other parameters were estimated using the opinions of experts from the literature, rather than experimental data. If more data could be collected to better parameterise the recovery, disease-induced mortality and restocking rates, then this would improve model accuracy.

4.6 CONCLUSION

In contrast to Chapter 2, the deterministic and stochastic model output are confirmed to be from the same distribution as seen in experimental data by Berriatua et al. (1999) when using Parameter Set 1. This gives confidence in the model structure. However, when parameters are added which might be important in long

term dynamics (Parameter Set 2) these had a larger impact on the initial stages of the outbreak, while the long term dynamics were similar to those seen when Parameter Set 1 was used. Therefore, Parameter Set 2 may not be suitable to use for long term dynamics. The initial stages of the outbreak were impacted by the flock size, with a flock becoming infected faster if the flock size was larger. This Chapter gives more insight into the parameterisation and structure of the within-farm model of sheep scab, which is used when attempting to improve the between-farm model (Chapter 5).

Chapter 5

AN EXPANDED MODEL OF TRANSMISSION OF SHEEP SCAB ACROSS GREAT BRITAIN

SUMMARY

In this chapter, the within-flock transmission model from Chapter 4 is extended to include transmission between neighbouring sheep holdings and via long distance sheep movements. Sheep movement and agricultural survey data provided by DEFRA from 2010 are used to capture realistic movement patterns. The published data from French et al. (1999) described in Chapter 3 is re-analysed here to identify summary measures that can be used for model fitting. SMC- ABC is then used to estimate three model parameters: the environmental pressure per infected individual (α), the decay rate of the environmental infectious pressure (β) and the indirect transmission rate from the environmental compartment *j* to susceptible sheep in holding *i* (υ_j). The fitted model is able to capture the number of farms infected in a year as well as seasonal patterns. The seasonal patterns in the model most closely match the years in the data when an autumn dip was used (which is the same treatment method used in the model simulations). This provides new evidence on the importance of the timing and synchrony of scab treatment. In addition, more evidence is provided for the importance of long-distance movements of sheep in the transmission of sheep scab.

5.1 INTRODUCTION

5.1.1 Rationale for expanding the Chapter 3 model

Although the Chapter 3 model gave some interesting insights about how sheep scab might spread through clusters of highly connected neighbouring farms, when comparing the spatial and quantitative model results with reported data (the MAFF data, described in full in Chapter 3 and in French et al., 1999), there were some discrepancies between the model and the data.

Firstly, although disease was introduced in the model into the same holdings that were infected at the start of the reported data, the spatial spread of disease was different between the model and the data. In randomly selected simulation results, there were only cases present in the same counties in the same year in the simulation as in the reported data in 27.9% of instances. The pattern of spatial spread was very different; in the model, disease only transmitted from the initially infected farms through clusters of highly connected neighbouring farms and then was limited to the edge of these clusters. However, in the reported data, the spatial location of reported cases appeared to be more dispersed from the location of the original introduction. It was inferred that this would be due to the fact that the model did not contain long distance movements. Therefore, long distance movements are added to the model in the current chapter in order to investigate whether this could explain the differences in the spatial patterns between the model and the data in Chapter 3.

There were also discrepancies between the quantitative results for the model and the data, with the model output having a greater incidence than observed in the data used for comparison. One explanation for this difference could be that no treatment for scab was used in the model, while the reported data were from years where treatments were used to prevent and treat scab (1973-1992) (French et al., 1999). Therefore, treatment is included in the model here to allow for a more accurate quantitative comparison. Since French et al. (1999) suggest that the seasonal dynamics of scab might be explained by the timings of treatment, the transmission rate is not scaled seasonally here, although this could also be an explanation for the higher incidence in the model results seen in Chapter 3.

Another reason for a higher incidence in the model results when compared to the data could be related to the parameterisation and structure of the within-farm transmission aspects of the model. The parameters and compartments used in the Chapter 3 model were the same as those used in Chapter 2 within-farm model, which was not statistically similar to the experimental data used for comparison (Berriatua et al., 1999) under those parameters. In Chapter 4, the addition of a carrier compartment and a parameter set which fits the conditions of the experimental data (Parameter Set 1) does lead to statistically similar results between the model and the data. Although another parameter set (Parameter Set 2) was also explored in Chapter 4 using data estimated from other sources, these did not seem to be important in longer term dynamics and did not fit the experimental data. Therefore, the majority of the parameter values used in the current chapter are from Parameter Set 1. A carrier compartment is also included here.

The flock sizes in the experimental trials (6-10 sheep) (Berriatua et al., 1999) were not reflective of the majority of sheep flocks in Great Britain (mean =335 sheep per flock). The Chapter 3 model was density dependent, with the area of all holdings assumed to be equal. However, as shown in Chapter 4, a flock of 200 sheep has faster transmission than a flock size of 9 and therefore, having a density dependent model and assuming the same area between holdings may have been one of the reasons for the higher incidence seen in the model results in Chapter 3 when compared to data. As the area of individual sheep holdings in Great Britain was not available, it was decided to assume in the model here that the area of a holding is scaled according to the flock size.

5.1.2 Model software choices

In order to add in these extra features, it was decided that STEM would no longer be a suitable software to use. As discussed in Chapter 3 (section 3.4.5.3), although STEM performs well when used at smaller scales, such as the within-farm model in Chapter 2 or in the stochastic Ebola model presented by Nieddu et al. (2017), the more subpopulations and events added to the model, the less well STEM performs. Attempts were made to add in long distance movements and treatments into the existing model in STEM, however, the workarounds needed for the treatments in

STEM meant there was limited flexibility in how these could be implemented and the addition of very few long distance movements significantly increased the running time.

The R package "SimInf" (Widgren et al., 2019) was chosen as a suitable alternative for the model presented in this Chapter. This package provides a flexible framework for building metapopulation spatio-temporal disease transmission models that can efficiently incorporate movement and demographic data. Within each subpopulation in the metapopulation model, infection dynamics are integrated as continuous-time Markov chains (CTMC) using the Gillespie stochastic simulation algorithm (Gillespie, 1977). Births, deaths and movements are scheduled events which modify the state of a subpopulation at a specified time point and are therefore deterministic in nature. SimInf uses compiled C code for the numerical solvers, rather than interpreted R code, which reduces computation time. In addition, the use of OpenMP (OpenMP Architecture Review Board 2008) allows for computations to be performed in parallel. The structure of the SimInf framework, which distinguishes between "global" (data which is shared among all subpopulations) and "local" (data which is specific to individual subpopulations), allows for easier formulation of complex models. There are also built in functions which can easily summarise the model results, for example the prevalence() function and the trajectory() function (Widgren et al., 2019).

The R software is more widely used by epidemiologists than STEM and therefore models built in R can be used and adapted by many other epidemiologists. There are also multiple packages which can be used alongside each other, for example, in this Chapter, ABC is able to be performed on the model built using SimInf with the EasyABC package (Jabot et al., 2015). Although policy makers are able to easily adapt and visualise spatial simulation models of transmission in STEM, this could be possible with the model presented here in future with development of a web R shiny app (Chang et al., 2017) and using R packages for animating data such as gganimate (Pedersen et al., 2019).

5.1.3 Model fitting and parameter estimation

In previous chapters of this thesis, model parameters were estimated using data from the literature and some of these values are used here. However, there are some new parameters within the SimInf framework where there is limited or no data for parameter estimation for sheep scab and so the posterior distributions of these parameters were estimated using Approximate Bayesian Computation (ABC).

Within the Bayesian framework, contrary to classical statistics, parameters are not considered to be fixed and instead are treated as random variables that follow a probability distribution. Where there are limited data available to fit a model, the Bayesian framework can therefore be used to estimate the probability distribution of the parameters given the data using Bayes rule:

$$P(\theta|D) = \frac{P(D|\theta)P(\theta)}{P(D)} \quad 5.1$$

where θ are the model parameters and D are the data, $P(\theta)$ is the prior belief, $P(D)$ is the marginal likelihood of the data, $P(\theta|D)$ is the posterior probability and $P(D|\theta)$ is the probability density function for the data given the parameters (the likelihood function) (Minter & Retkute, 2019).

Where a likelihood function is not available, Approximate Bayesian Computation (ABC) can be used to estimate the posterior probability ($P(\theta|D)$) by using a simulation-based procedure (Pritchard et al., 1999; Beaumont et al., 2002; Marjoram et al., 2003; Sisson et al., 2007). All of these ABC methods have the following common form (adapted from Toni et al., 2009):

1. Sample candidate parameter values ($\theta*$) from a proposed distribution ($P(\theta)$)
2. Run a model simulation to produce dataset (D*) which is described by the conditional probability distribution ($P(D|\theta)$)

3. Compare the simulation dataset (D*) with the reported data (D_0) using a distance function (*d)* and a desired level of agreement between D* and D_0 (tolerance, *T*)

In some cases, a distance function (*d*) may not be able to be defined between full datasets and in these cases, it can be defined based on summary statistics space of the simulation data (S(D*)) and reported data ($S(D_0)$).

The ABC rejection sampler algorithm developed by Pritchard et al. (1999) is the simplest algorithm, however it has the disadvantage of having a low acceptance rate if the prior distribution varies greatly to the posterior distribution. An ABC method using Markov chain Monte Carlo (ABC MCMC) has been developed to avoid this issue (Marjoram et al., 2003). However, this can still be inefficient due to long chains and chains getting stuck in low probability regions. The efficiency can be improved by use of an ABC method based on sequential Monte Carlo (ABC SMC) first developed by Sisson et al. (2007). It achieves this by approximating the posterior in a progressive manner, whereby sequential samples are derived from $D^{*(t-1)}$ as shown:

$$D^{*(t)} = (\theta_i^{(t)})_{i=1}, \ldots, N \qquad 5.2$$

and the set of tolerance levels are decreasing $\{T_1,\ldots,T_T\}$. This improves efficiency by ensuring that more sampling is carried out in the areas of high likelihood within the parameter space, hence avoiding systematic sampling within the whole parameter space (Lenormand et al., 2013).

The original ABC SMC method by Sisson et al. (2007) has been improved upon by Toni et al. (2009), Beaumont et al. (2009), Drovandi and Pettitt (2011), Del Moral et al. (2012) and Lenormand et al. (2013). The algorithm proposed by Lenormand et al. (2013) was shown to be the most efficient when applied to a toy example and a complex social model (Lenormand et al., 2013) and therefore is the method used for the ABC presented in this chapter.

5.2 AIMS

The main purpose of the current chapter is to investigate why the spatial and quantitative discrepancies between the Chapter 3 model and the reported data may have occurred. An additional aim was to improve the Chapter 3 model to allow for more flexibility and a faster running time, in order to future-proof the model and enable it to be more useful in future analyses.

5.3 METHODS

5.3.1 Model description

The model in this chapter was an adaptation of the SISe_sp model from the "SimInf" package, described fully in Widgren et al., 2018 and Widgren et al., 2019. (the adapted model shall be known in this thesis as the SICTDe_sp model). The original SISe_sp model is a metapopulation model, built to model the spread of Verotoxigenic Escherichia coli O157:H7 (VTEC O157) between cattle herds in Sweden (Widgren et al., 2018) and adapted from the SISe model previously described by Bauer et al. (2016) and Widgren et al. (2016). The SISe_sp function in the SimInf package was adapted here to incorporate aspects of the within-farm sheep scab model from Chapter 4 and used to model transmission of scab between farms in Great Britain. The adapted c and r code for the adapted SISe_sp function (the SICTDe_sp function) described here can be found in the Appendix with highlighted changes. The changes to the code in the SimInf package were made and installed locally.

Between-farm transmission was assumed to occur due to movements of sheep between holdings and between neighbouring farms up to 2km from each other. Sheep movements are modelled as scheduled events in the SICTDe_sp function using DEFRA sheep movement data from 2010 (fully described in section 5.3.2.3 and 5.3.4.1). Between-farm transmission for neighbouring farms occurs between farms that are within a 2km distance from each other as described in Chapter 3. However, the difference here is that the transmission term is scaled according to distance, whereas the transmission between farms up to 2km away was assumed to be the same regardless of distance in the Chapter 3 model.

The model compartments here are the same as described in the within-farm model in Chapter 4 (N = S + I + C + T, D is not a true compartment), however, there is an additional environmental compartment (E), which can be contaminated with free living pathogens by infected and carriers. Here the pathogens are *P.ovis* mites. Rather than becoming infected via direct contact as seen in the Chapter 2, 3 and 4 models, susceptible animals become infected via transmission from the environmental compartment, which has an infectious pressure determined by pathogen shedding (in this case the pathogen is *P.ovis* mites), by infected or carrier sheep within the same flock or from infected and carrier sheep from a geographically close flock. This time-dependent environmental infectious pressure $\varphi_{i(t)}$ is used to model the environmental compartment within each holding *i* at time *t* and was assumed to be uniformly distributed within each holding. The area of the holding is assumed to be proportional to the number of individuals within the holding.

The following equation describes the rate of change of the environmental infectious pressure $\varphi_{i(t)}$ over time:

$$\frac{d\varphi_i}{dt} = \frac{\alpha I_i(t) + \varepsilon\alpha C_i(t)}{N_i(t)} + \sum_k \frac{\varphi k(t) N_k(t) - \varphi i(t) N_i(t)}{N_i(t)} * \frac{D}{d_{ik}} - \beta(t)\varphi i(t) \qquad 5.3$$

Where *i* is a sheep holding and *k* is a sheep holding that is considered to be geographically close to *i* such that transmission of scab between the holdings is possible. The environmental infectious pressure from geographically close holdings was assumed to decrease as the magnitude of the Euclidean distance between holdings (d_{ik}) increased. It was also assumed to never be greater than the within-farm transmission. The parameters in this equation are defined in Table 5.1. Equation 5.3 is adapted from the equation used by Widgren et al. (2018) to incorporate a carrier with the addition of $\varepsilon\alpha C_i(t)$ which includes a scaling rate for the transmission rate for Carriers on the shedding rate for Infectious individuals (α). This is the equivalent of having the movement of susceptibles to infecteds calculated by $(\beta I + \varepsilon\beta C)S$ in the Chapter 4 model.

Table 5.1 The parameters in the SICTDe_sp model

Parameter	Description
α	The daily rate of *P.ovis* shedding per infected individual that contributed to environmental infectious pressure (note this symbol is not used for the restocking rate as seen in Chapter 4)
ε	The scaling rate for the contribution of carriers to environmental infectious pressure
D	Spatial coupling between holding *i* and neighbour *k*
d_{ik}	The Euclidean distance between holding *i* and neighbour *k*
I_i	The number of infected sheep at holding *i*
C_i	The number of carriers at holding *i*
N_i	The total number of sheep in all compartments ($S_i + I_i + C_i + D_i + T_i$).
β	The decay rate of the environmental infectious pressure
υ_j	The indirect transmission rate from the environmental compartment *j* to susceptible sheep in holding *i*
γ	Recovery rate for infected sheep
q	The proportion of acute infections that become carriers (q)
m	Disease mortality rate
τ	Recovery rate for carriers
ω	Restocking rate (note this was ξ in Chapters 2 and 3 and α in Chapter 4).

The direction and nature of the transitions between the compartments is the same as between the compartments in Chapter 4, with the exception of the transition from the Susceptible to the Infected compartment which is dependent on the concentration of environmental infectious pressure in holding i ($\varphi_{i(t)}$) and the indirect transmission rate from the environment to sheep (υ_j) :

$$S_{ij} \xrightarrow{\upsilon_j \varphi_i} I_{ij}$$

$$I_{ij} \xrightarrow{\gamma(1-q)} S_{ij}$$

$$I_{ij} \xrightarrow{\gamma q} C_{ij}$$

$$I_{ij} \xrightarrow{m} D_{ij}$$

$$C_{ij} \xrightarrow{\tau} S_{ij}$$

$$D_{ij} \xrightarrow{\omega} S_{ij}$$

All transitions were modelled as continuous-time discrete Markov chains (CTMC) using the Direct Method (Gillespie, 1977). The parameters are given in Table 5.1.

Treatment of sheep (internal movements of sheep within each holding from the S, I and C compartments to the T compartment) and end of protection of treatment (internal movements of sheep from the T compartment to the S compartment) are incorporated as events in SimInf (described in section 5.3.4.4) and are therefore not included in the daily transitions between compartments. The natural birth and death rate parameter, μ, from the model in Chapter 4 is not included in the model here as births and deaths can be modelled as events in SimInf (although none are included in any simulations presented here, since the model output was found to not be sensitive to these in Chapter 4). A full description of how events (births, deaths, movements and treatment) are implemented in SimInf is given in Widgren et al. (2019) (and in the supplementary material of their paper).

5.3.2 Input data

5.3.2.1 Agricultural survey data (2010)

Agricultural survey data from 2010 for England, Wales and Scotland was used along with the sheep movement data to calculate the initial number of sheep at each holding at the start of the model simulation (section 5.3.4.1). The data were provided by DEFRA.

The data on number of sheep at each individual holding in England and Wales were taken from the June Census of Agriculture and Horticulture in 2010 which was carried out under EU legislation. The data were collected via a postal survey, although there was an option to complete the survey online. The response rate in England was 73% (n = 127,000) and 64.5% in Wales (n= 22,300). The survey collected data from farms which have "commercial" levels of farming activity based on their most recent June survey response. This included farms that contained more than 5 hectares of agricultural land and had at least 20 sheep (according to the EU Farm Structure Survey Regulation EC 1166/2008). This excluded 40% of registered holdings in England, which are therefore not included in the model, however, the sum of all sheep across these holdings make up less than 1% of the national total of sheep (DEFRA, 2010).

The data on the number of sheep at individual holdings in Scotland were taken from the annual June Agricultural Census managed by the Rural and Environmental Analytical Services Division of the Scottish Government. This is a combination of data from the Single Application Form database for holdings claiming a Single Farm Payment (n = 25,000, response rate 74%) and data from a census of the remaining holdings (n = 12,000, response rate 55%) which were under the same EU threshold for commercial farming already specified for England (DEFRA, 2010).

5.3.2.2 MAFF data

Data on the number of reported cases of sheep scab in Great Britain from 1973-1992 are used here to initialise and fit the model. This data is fully described in Chapter 3, section 3.3.4.1 and are presented in French et al. (1999). The data were originally provided by the Ministry of Agriculture, Fisheries and Food (MAFF).

Although the data were not from the same years as the agricultural survey or the sheep movement data (2010), sheep scab has not been notifiable across the whole of Great Britain since 1992 (MAFF, 1992; ADAS, 2008) and therefore it is thought that the data prior to 1992 would be more reliable. In addition, treatment strategies are now the responsibility of the individual farmer (although according to the Sheep Scab Order 1997, it is still compulsory to treat when scab is detected), whereas during 1973-1992 a number of national programs were implemented. The nature of treatment practices since 1992 date are much less known and therefore it was decided that implementing a national treatment strategy in the model was a sensible first step when testing the model and can more reliably be compared to the years when national control occurred.

There were four different treatment strategies employed across 1973-1992. Table 5.2 describes these strategies and gives the years that these took place. Fig. 5.1 shows the mean daily number of cases across all the years that each strategy took place. It appears that in the years an autumn dip was not used, the number of cases in the winter were greater (Fig. 5.1.).

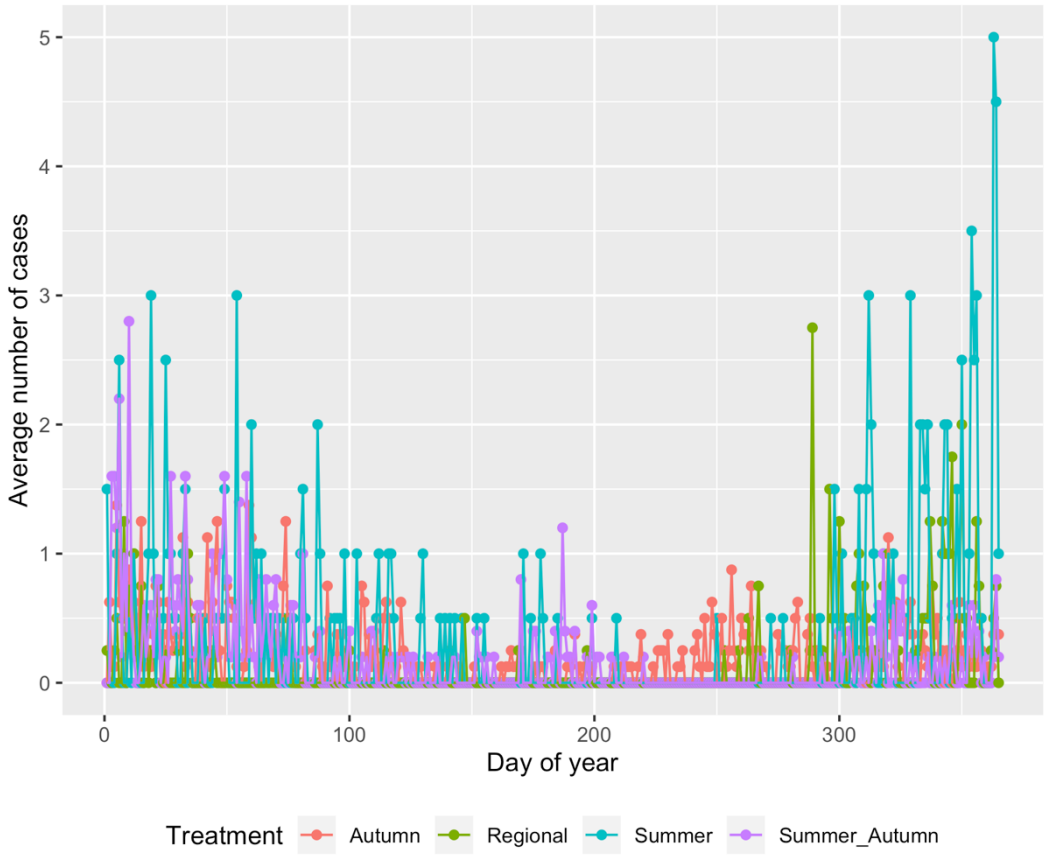


Fig. 5.1 The mean daily number of cases of scab in a one-year period when four different treatment strategies were employed according to MAFF data from 1973-1992. The treatment strategies are fully described in Table 5.2. The mean number of cases per day was taken across all years that a particular strategy was employed.

Table 5.2 Control measures for sheep scab in Great Britain from 1973 to 1992.
The information in this table is taken from Fig.1, French et al. (1999) unless specified otherwise.

Years control measure was in place	Control measure	Details
1973-1975	Initial outbreak response (Loxam, 1974) and regional dipping	Tracing, dipping and movement restrictions for infected sheep and nearby farms.
1976-1979 1981 1989-1992	National autumn dip	According to the Sheep Scab (National Dip) Order 1990, this must occur during the period of six weeks following the 23rd September in any year.
1980	Regional dip	This meant that local authorities were able to enforce dipping where outbreaks of scab in their region had been identified.
1982-1983	National summer dip	No specific dates are provided on this, but it is assumed that this happened for a period of six weeks around June, as this is when shearing and worm - drenching occurred.
1984-1988	National summer and autumn dipping	Dipping occurred both in the autumn and summer as previously described

5.3.2.3 Sheep movement data (2010)

Chapter 3 suggested that without long distance movements, scab would only spread throughout clusters of highly connected farms and spread no further once they reach the edge of the cluster. However, with long distance movements, it is expected that scab will spread to a wider range of locations as seen with the MAFF data. Therefore, long distance movements are included in the model presented here. These were included as external events using sheep movement data.

5.3.2.3.1 Background about the sheep movement data

Data on sheep movements in Great Britain during 2010 were provided by the DEFRA. These data were a combination of sheep movements recorded in the Animal Movement Licensing System (AMLS) maintained and administered by DEFRA and the Scottish Animal Movement System (SAMS) which is run by the Scottish Executive Environment and Rural Affairs Department (SEERAD). In 2010, sheep movements in England, Wales and Scotland were required to be recorded in accordance with the Sheep and Goats (Records, Identification and Movement) Order 2009.

The data provided contained one row per movement, with columns describing the date of the movement, the location of the departure holding and the destination holding, the number of days over which the movement took place and the number of sheep moved (Table 5.3).

Table 5.3 The column names in the sheep movement data and their assumed meanings

Name of column	Description of data
movdate	Date of movement
depcph	CPH number of departure location
destcph	CPH number of destination location
deploctype	Location type of departure location
destloctype	Location type of destination location
depcounty	County of departure location
destcounty	County of destination location
depeast	Easting of departure location
depnorth	Northing of departure location
desteast	Easting of destination location
destnorth	Northing of destination location
nummovdays	The number of days to transport sheep from depcph to destcph
nummovs	Assumed to be the number of batches of sheep
numsheep	Number of sheep moved from depcph to destcph

5.3.2.3.2 Processing the sheep movement data

All movements where the number of sheep moved was zero were removed.

The unique values in the column "nummovdays" was 1,2,3. This was assumed to be the number of days it took to transport the sheep. In the model, for simplicity, it was assumed that all sheep moved from their departure CPH to their destination CPH in one day and therefore data from the "nummovdays" column was not included.

The meaning of the column "nummovs" was unknown, however, was assumed to be the number of batches since the holding with the highest value in the "nummovs" column (n = 140) was from a mart to a slaughterhouse. The other values in the "nummovs" column that were greater than 1 were generally from a gathering to a slaughterhouse or to animal residences. The mode value (and the 3rd Quartile) in this column was 1. Data from this column were also not included in the model, since the total number of sheep moved was provided and the number of batches were thought to be unimportant, if they occur at the same time and between the same two locations.

The movements were implemented into the model as a scheduled event (implementation of scheduled events in SimInf is fully described in Widgren et al. 2019). A data frame within R was made with a row for each movement and columns as described in Table 5.4.

Table 5.4 Explanation of the data frame used to implement movements as scheduled events in SimInf

Column name	event	time	node	dest	n	proportion	select	shift
Example	extTrans	269	1	2	150	0	4	0
Explanation	Type of event – here this is an external transmission event because sheep are moved between two holdings	Day of model simulation that event happens	The node ID of the departure holding	The node ID of the destination holding.	The number of sheep moved. This is the number specified in the movement data	Using actual number of sheep here is desired (n column) so this is 0.	This refers to column 4 from the E matrix in the r code in the Appendix which specifies that the movement happens from compartments S, I, C and T	This is only used for internal transmission events

5.3.2.3.3 Exploring the sheep movement data

The smallest batch of sheep moved was 1 and the largest batch of sheep moved was 5826. From January to July, the number of sheep moved was fairly consistent, ranging from 2.1-2.9 million per month (Fig. 5.1). There was an increase in the number of sheep moved in August to 3.9 million and September was the month where the most sheep were moved (5.4 million). A large number were still moved in October (4.9 million) and November (4.2 million), with 3.1 sheep moved in December (Fig. 5.1). The distance moved for each recorded movement was calculated using the easting and northing values. The mean recorded movement by a batch of sheep was 64km (range 0-1118km). For each recorded movement, the number of sheep in the batch was multiplied by the distance moved by the batch. The result was added together with results from all other movements in the same month (Fig. 5.2). As expected, this showed a similar pattern to Fig. 5.1 (which shows just the number of sheep moved), with lower distances in January to July (ranging from 147 million km to 224 million km), with an increase in August to 297 million km, a peak in September (441 million km) and decrease from October (372 million km) to December (239 million km). This seasonal pattern of movements may impact the transmission dynamics of sheep scab across Great Britain, since as more movements occur, the risk of transmission between farms increases.

The most common departure location type was an animal residence (farm) (Fig. 5.3). There were also a large number of unknown departure location types and a large number of movements from gatherings. The most common destination location was a gathering, followed by animal residences, slaughter premises and slaughterhouses and agricultural holdings.

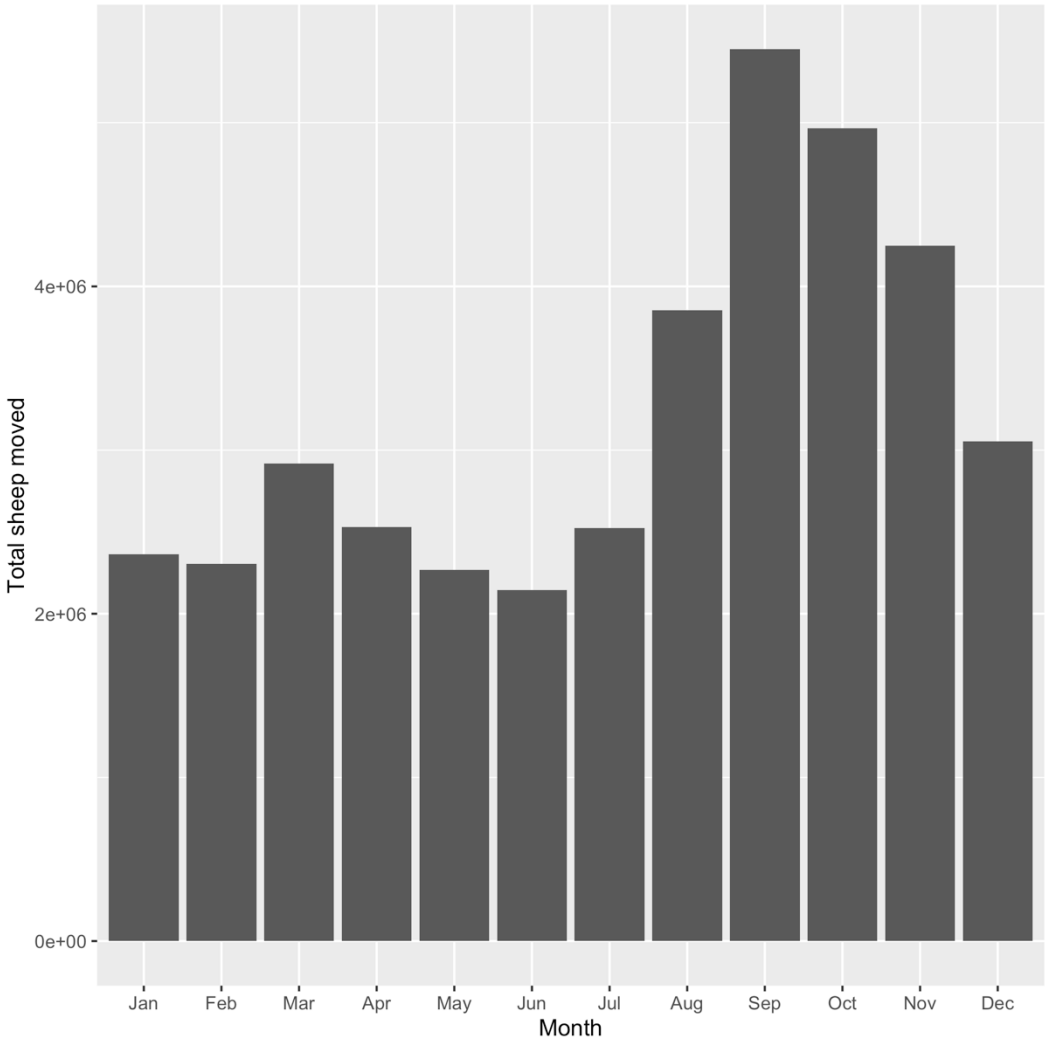


Fig. 5.2 The total number of sheep moved by month in 2010 according to sheep movement data

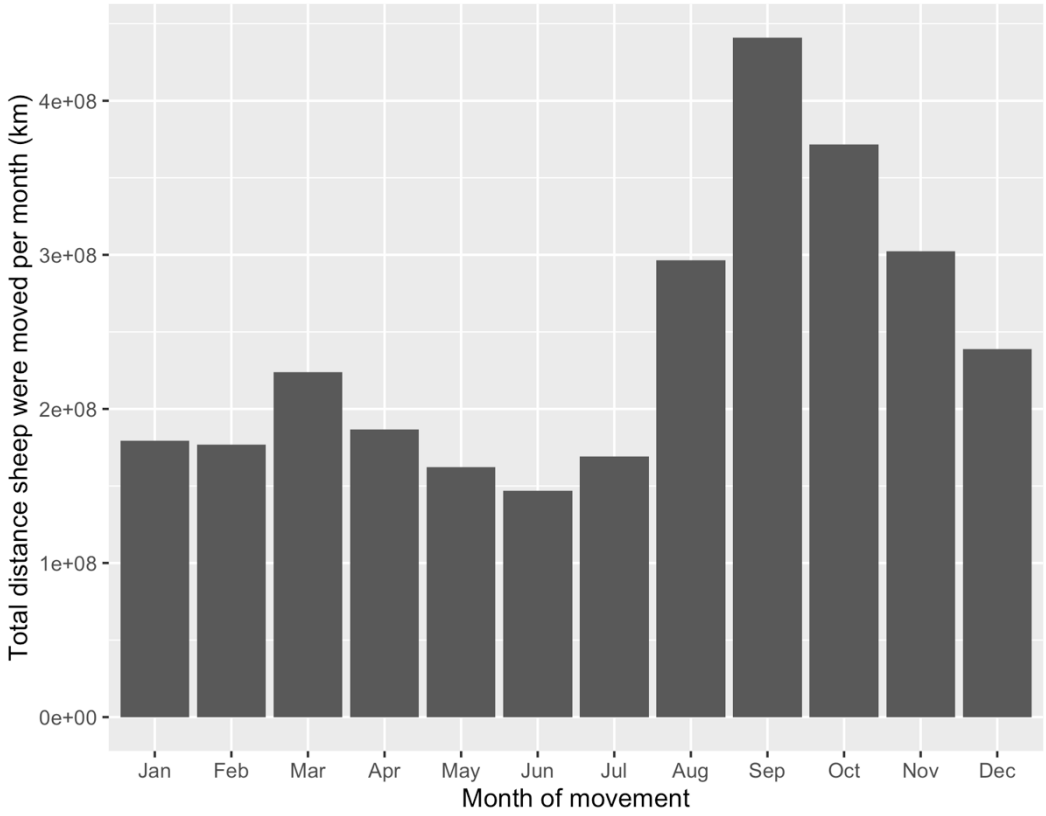


Figure 5.3 The sum of all distances individual sheep were moved, by month in 2010, according to sheep movement data. For each recorded movement, the number of sheep was multiplied by the distance moved. The result was added together with results from all other movements in the same month.

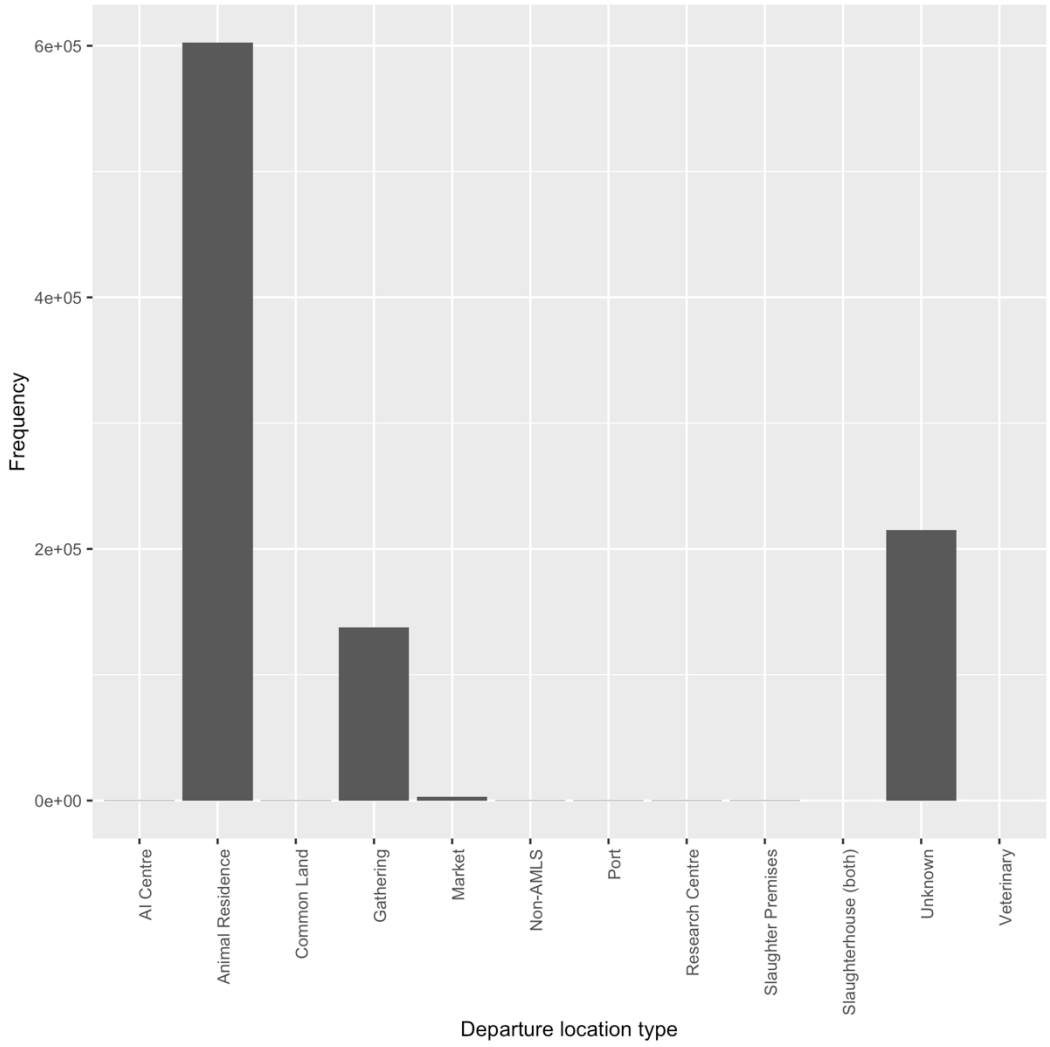


Fig. 5.4 The frequency of the types of locations sheep were moved from in 2010 according to sheep movement data

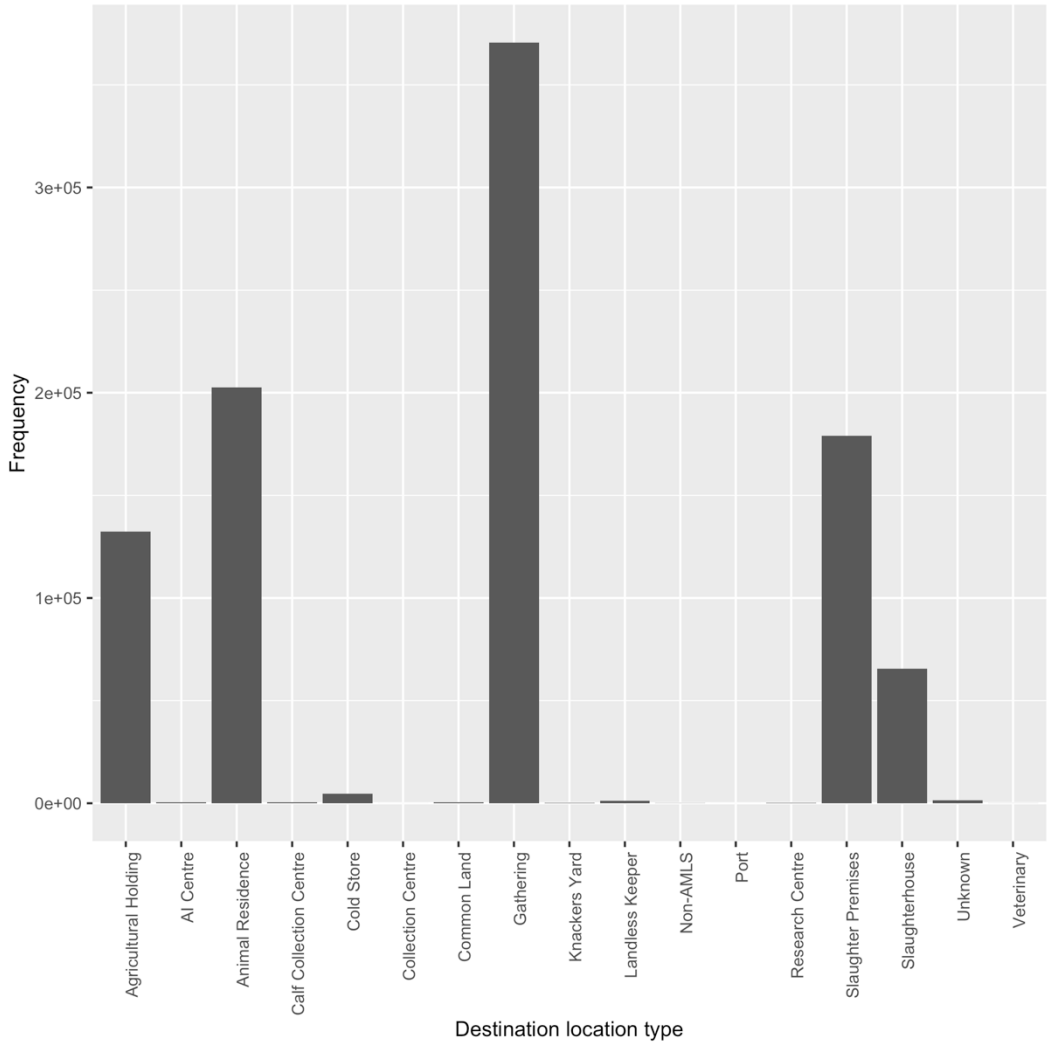


Fig. 5.5 The frequency of the types of locations sheep were moved to in 2010 according to sheep movement data

5.3.3 Parameter estimation

In Chapter 4, a parameter set which fits the conditions of the experimental data (Parameter Set 1) gives statistically similar model results when compared to the data. Although another parameter set (Parameter Set 2) was also explored in Chapter 4 using data estimated from other sources, these did not seem to be important in longer term dynamics and did not fit the experimental data. Therefore, the majority of the parameter values used in the current chapter are from Parameter Set 1 in Chapter 4.

However, the SISe_sp model from the SimInf package incorporates transmission within and between farms differently to the models previously described in this thesis. As described in section 5.3.1, transmission is now modelled indirectly via an environmental compartment and so there are four new parameters: the daily contribution to environmental pressure per infected individual (α), the decay rate of the environmental infectious pressure (β), the indirect transmission rate from the environmental compartment *j* to susceptible sheep in holding *i* (υ_j) and spatial coupling (*D)*. Since there is limited data available on these parameters and as they are likely to be sensitive to the model (since the transmission rate in Chapters 2 and 4 was the most sensitive to model output), a posterior distribution was estimated for α, β and υ_j using ABC SMC. The spatial coupling (*D*) was estimated using a different method which is fully described in section 5.3.3.2.

5.3.3.1 Estimating the prior distributions for α, β and υ_j

For each parameter (α, β and υ_j), a one-at-a-time sensitivity analysis (OAT SA) was performed where the model was run repeatedly for different values of the parameter of interest under the conditions described in section 5.3.4. For each OAT SA, the model was run 5 times with different seeds. The yearly incidence from the model outputs were then compared to the yearly incidence from 1976 in the MAFF data (101 new outbreaks) using the Poisson Log Likelihood:

$$\text{data}*\log(\text{model}) - \text{model} \qquad 5.4$$

The values of the unknown parameters (α, β and υ_j) when they were not the parameter of interest were estimated prior to performing the OAT SA by running the model until the estimates for these parameters gave yearly incidence results which were the same order of magnitude as the yearly incidence from 1976 in the MAFF data (101 new outbreaks). The best estimates were 0.004 for α, 0.07 for β and 0.012 for upsilon. All other parameters used were as described in Table 5.5.

In the OAT SA for α (the daily contribution to environmental pressure per infected individual), α was varied from 0.001 to 0.02. by 0.001. The Poisson log likelihood suggests that the model output deviates the least from the data when α is within the range of 0 to 0.012 (Fig. 5.5). Therefore, in the ABC SMC, the prior distribution for α is a uniform distribution with a minimum value of 0 and a maximum value of 0.012 (Table 5.5).

In the OAT SA for β (the decay rate of the environmental infectious pressure), (β) was varied from 0 to 1 by 0.01 in an OAT SA and from 0 to 0.2 by 0.01. The Poisson log likelihood suggests that the model output deviates the least from the data when β is within the range of 0.07 to 0.1 (Fig. 5.6, Fig. 5.7). This distribution was reduced by looking at the death rate of *P.ovis* mites. Since the environmental infectious pressure captures direct and indirect transmission, it was assumed that individual *P.ovis* mites may survive on a host for a maximum of 40 days (Wall et al., 1999) or remain viable in the environment for 15 days (O'Brien et al., 1994). Therefore, it was assumed the decay rate for mites would not be much lower than 0.025 (1/40) or much greater than 0.07 (1/14). The prior distribution was therefore estimated to be uniform with a minimum value of 0.02 and a maximum value of 0.08.

In the OAT SA for υ_j (the indirect transmission rate from the environmental compartment *j* to susceptible sheep in holding *i*), υ_j was varied from 0 to 0.001 by 0.0001 in a OAT SA. The Poisson log likelihood suggests that the model output deviates the least from the data when υ_j is within the range of 0 to 0.0006 (Fig. 5.8). Therefore, in the ABC SMC, the prior distribution for α is a uniform distribution with a minimum value of 0 and a maximum value of 0.0006.

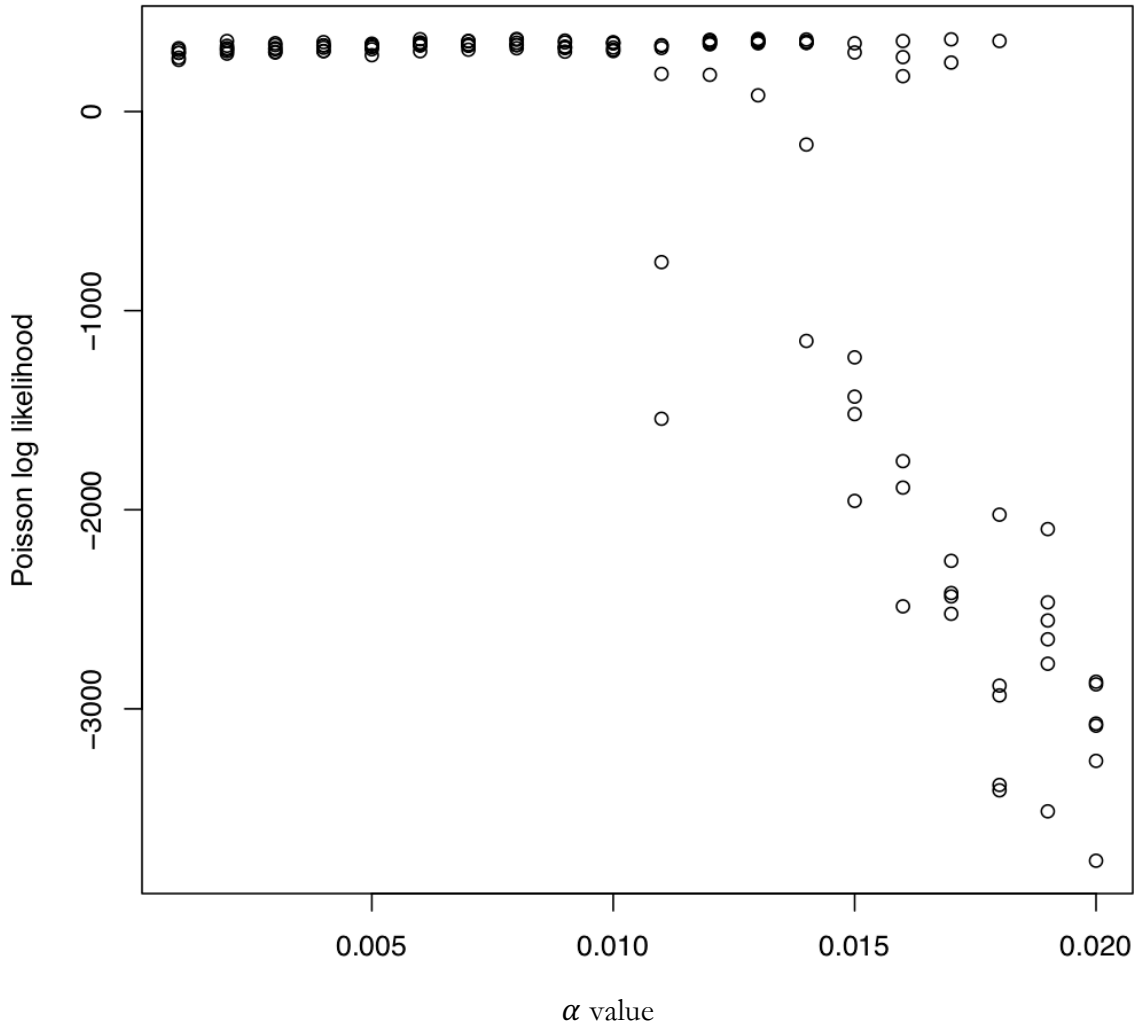


Fig. 5.6 Poisson log likelihood of yearly incidence between the model output and the MAFF data from 1976 when the daily contribution to environmental pressure per infected individual (α) is varied from 0 to 0.02 by 0.001 in one-at-a-time sensitivity analysis.

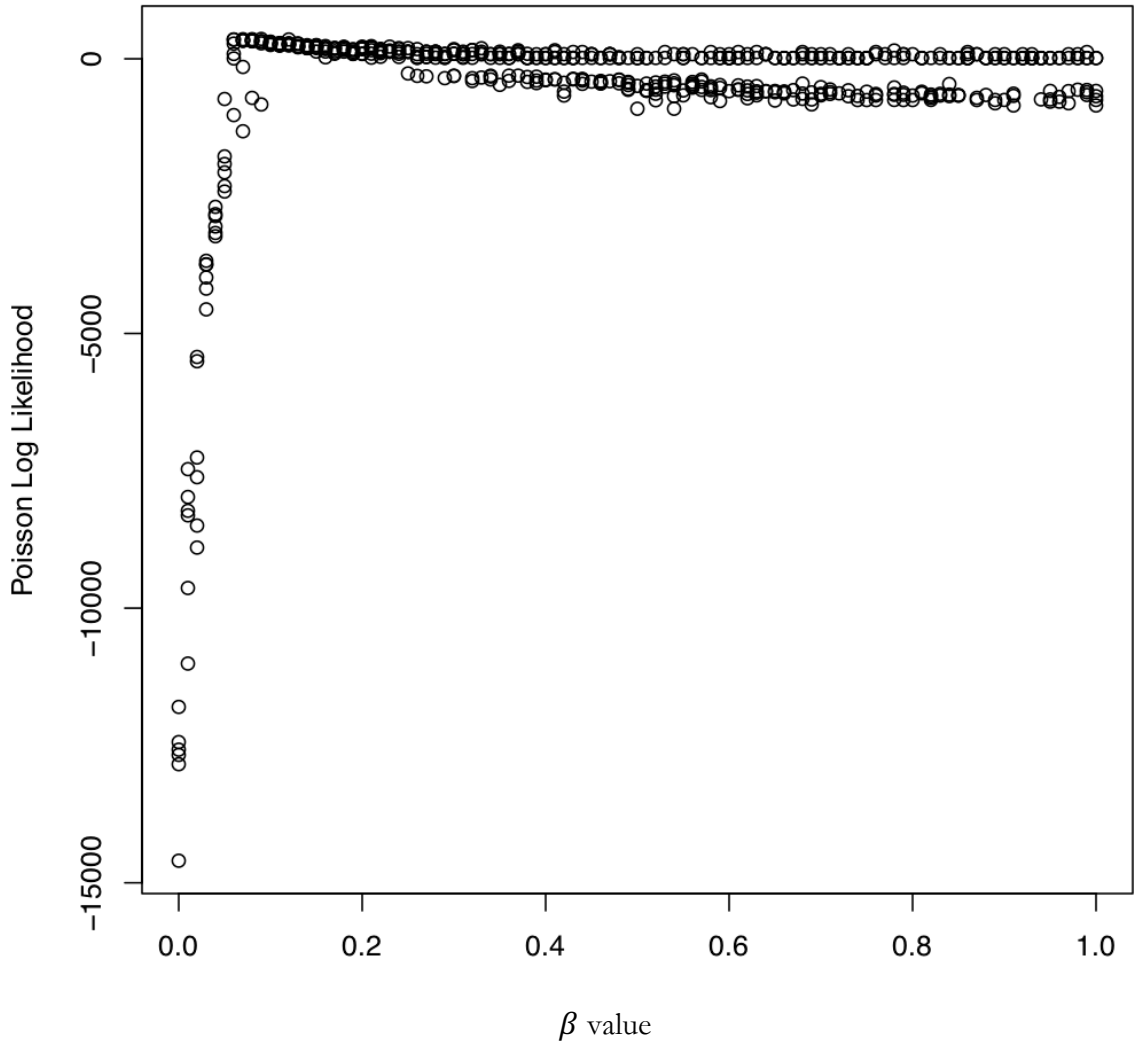


Fig. 5.7 Poisson log likelihood of yearly incidence between the model output and the MAFF data from 1976 when the decay rate of the environmental infectious pressure (β) is varied from 0 to 1 by 0.001 in one-at-a-time sensitivity analysis.

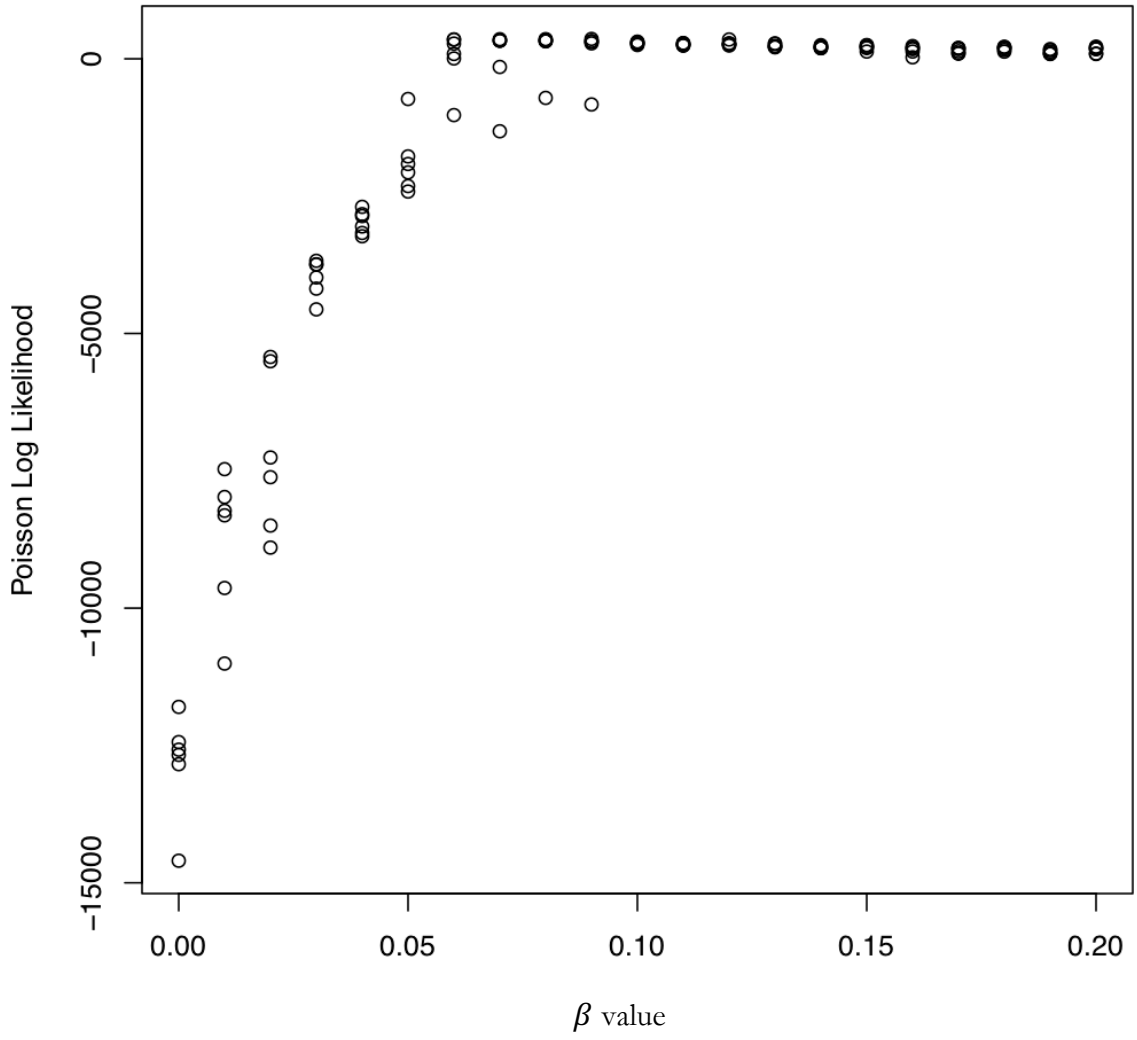


Fig. 5.8 Poisson log likelihood of yearly incidence between the model output and the MAFF data from 1976 when the decay rate of the environmental infectious pressure (β) is varied from 0 to 0.2 by 0.001 in one-at-a-time sensitivity analysis.

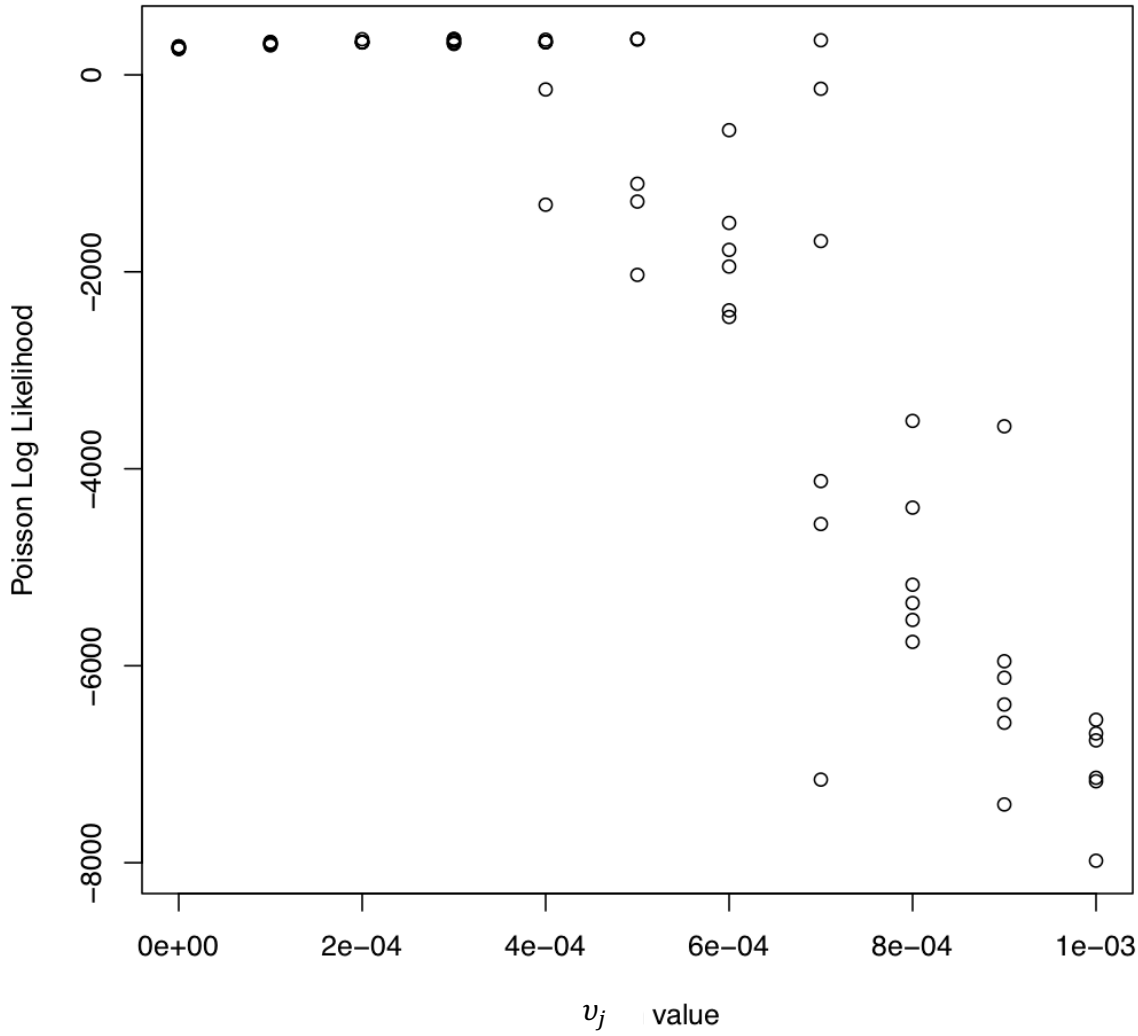


Fig. 5.9 Poisson log likelihood of yearly incidence between the model output and the MAFF data from 1976 when the indirect transmission rate from the environmental compartment j to susceptible sheep in holding i (v_j) is varied from 0 to 0.001 by 0.0001 in one-at-a-time sensitivity analysis.

5.3.3.2 Estimating the spatial coupling

The SimInf model has been written so the contribution to infectious pressure from a neighbouring farm *k* to farm *i* is scaled by a transmission multiplier that is based on the spatial coupling parameter (*D*) divided by the distance between the two holdings (d_{ik}) (Equation 5.3). The nature of this means that between-farm transmission via spatial proximity can never be greater than within-farm transmission.

The spatial coupling parameter (*D)* was modified in a one-at-a-time sensitivity analysis (from 0, to 1, by 0.05) while keeping all unknown parameters as described in section 5.3.3.1 ($\alpha = 0.0004$, $\upsilon_j = 0.012$ and $\beta = 0.07$) and all other parameters as shown in Table 5.5 (Fig. 5.10). A Poisson log likelihood (equation 5.4) comparing the yearly incidence results from the OAT SA for spatial coupling and the yearly incidence from 1976 in the MAFF data (101 new outbreaks) was carried out and the top 5% results presented (Fig. 5.10b). However, it was unclear from these results which range of the parameter value would be most suitable when using a Poisson Log Likelihood (equation 5.4). This result is similar to the result seen in a sensitivity analysis of the spatial coupling parameter in the original SISe_sp model by Widgren et al. (2018), where they also found that halving or doubling the value of *D* did not have a large impact on the model fit, however, removing it from the model did impact the model fit.

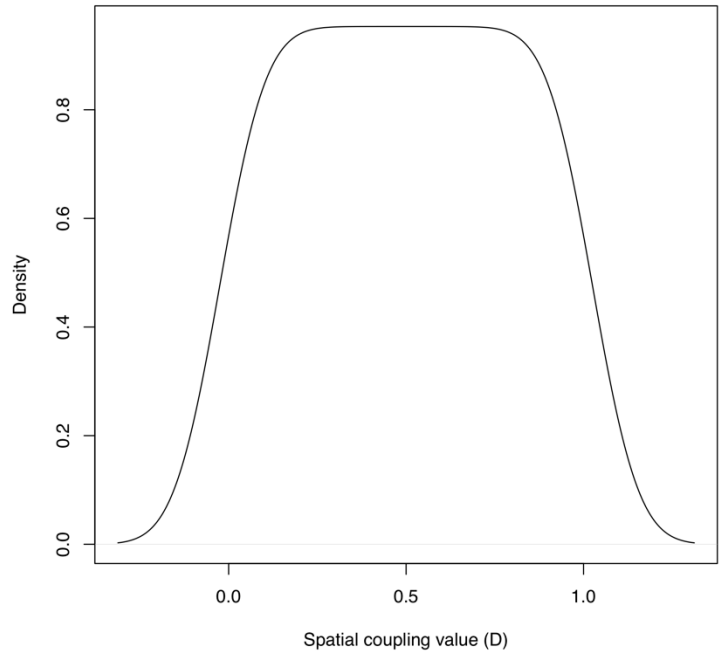
Therefore, it was decided here to use the mean of the top of the PLL results as the spatial coupling parameter (*D*) (0.5642857). Interestingly, this is a comparable value to the mixing rate between common grazing farms in Chapter 3 (0.5136), which, although is not applied in exactly the same way, also captures transmission between neighbouring farms.

Further investigation of the behaviour of D, demonstrates that the transmission scaling behaviour of this leads to farms greater than 10m away having a very low impact on between farm transmission relating to spatial proximity (Fig. 5.11). This is a limitation of the SimInf model presented here, as described in 5.3.4.1 it is assumed that farms up to 2km away from a farm contribute to transmission. This is still possible here, but at a very low rate. At the present time, it was difficult to modify

this in the SimInf code, as it is ingrained in a number of processes, but this is something that could be adapted in future versions of the sheep scab model presented here if it was found to be important.

However, it is assumed that the majority of between-farm transmission that is related to spatial proximity occurs due to grazing sheep from the same farms on local common grazing land. This is already captured in the model presented here via the scheduled events of sheep movements which include movements to and from common grazing areas (although movements to common grazing areas that border a holding may not be recorded, DEFRA, 2019a).

(a)



(b)

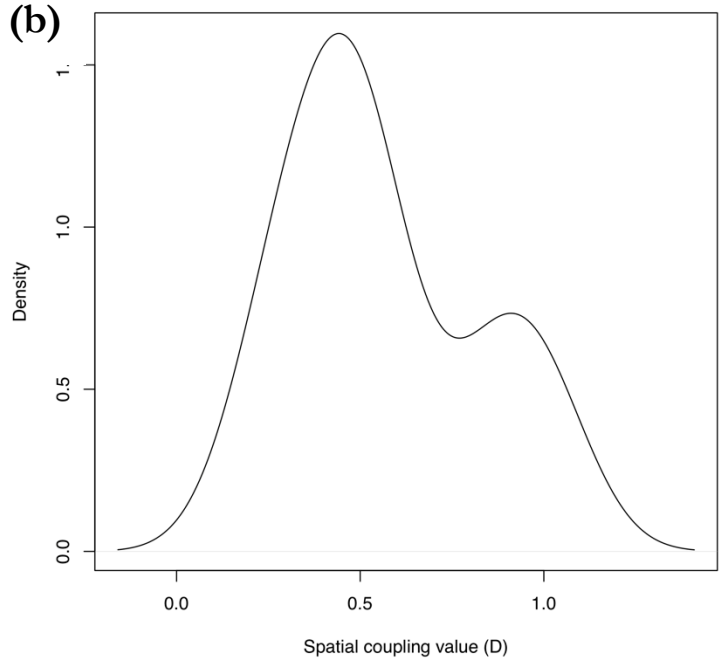


Fig. 5.10 Density of model output when the spatial coupling (D) is varied from 0 to 1 by 0.05 in one-at-a-time sensitivity analysis. (a) All results **(b)** Top 5% of results from a Poisson log likelihood of yearly incidence between the model output and the MAFF data from 1976

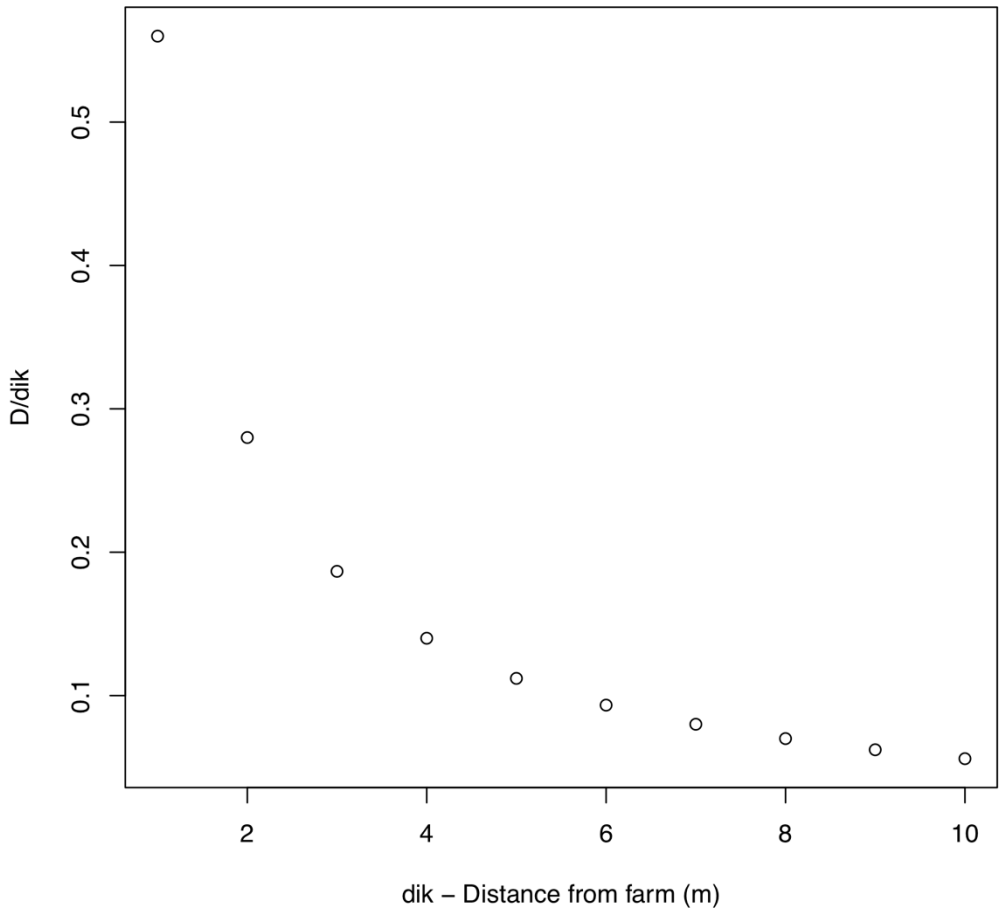


Fig. 5.11 The impact of varying distance between farms *i* and *k* (d_{ik}) on the between farm transmission multiplier (spatial coupling(D)/distance between farms i and k (d_{ik})) (equation 5.3)

Table 5.5 The parameter values (including the prior distribution where relevant) used in the SICTDe_sp model

Parameter	Description	Value	Description of source
α	the daily rate of *P.ovis* shedding per infected individual that contributed to environmental infectious pressure	Prior(0,0.012,uniform)	Section 5.3.3.1
ε	the scaling rate for the contribution of carriers to environmental infectious pressure	$\frac{1}{3}$	Parameter Set 1, Chapter 4
D	Spatial coupling between holding i and neighbour k	0.5642857	Section 5.3.3.2
β	The decay rate of the environmental infectious pressure	Prior(0.02, 0.08, uniform)	Section 5.3.3.1
υ_j	The indirect transmission rate from the environmental compartment j to susceptible sheep in holding i	Prior(0,0.0006,uniform)	Section 5.3.3.1
γ	Recovery rate for infected sheep	$\frac{1}{77}$	Parameter Set 1, Chapter 4
q	The proportion of acute infections that become carriers (q)	$\frac{1}{2}$	Parameter Set 1, Chapter 4

τ	Recovery rate for carriers	$\frac{1}{653}$	Parameter Set 1, Chapter 4
m	Disease mortality rate	0	Parameter Set 1, Chapter 4
ω	Restocking rate	0	Parameter Set 1, Chapter 4 (restocking rate is α in Chapter 4)

5.3.4 Initial model conditions

5.3.4.1 The number of sheep in each farm at the start of the simulation

The simulations in the chapter all start on the 1st January 2010. In order to establish the number of sheep at each farm on this date, the agricultural survey data from 2010 had to be reconciled with the sheep movement data. The number of sheep in the agricultural survey is taken in June and so is not equivalent to the number of sheep that would be present on the 1st January 2010 (the start date for the sheep movement data). In addition, there are additional holding types, such as markets, that were not included in the agricultural survey, which have movements to and from them in the movement data.

Therefore, the number of sheep in each farm at the start of the simulation was estimated using both the agricultural survey data and the sheep movement data. This was done assuming that there were no natural births and deaths during the period of the simulation and ensuring that the number of sheep in a farm would never become negative at any point in the simulation. The two data sets had county-parish-holding (CPH) number as an identifier for holdings. The method for this is outlined below in five steps:

Step 1- Filtering the agricultural survey data for holdings that have at least 1 sheep. There were initially 209,881 holdings in the dataset. Of those holdings, there were 64836 that had at least 1 sheep and all of these had a unique CPH number. The only location type was "Agricultural holding".

Step 2- Adding CPHs which are in the movement data but not the agricultural survey data. Include all the CPH numbers that are not in the agricultural survey but are in the movement data in the survey list and allocate zero starting sheep in these holdings. There were 112,893 holdings in the dataset at the end of this step.

Step 3- Remove holdings where the eastings and northings were zero. After this adjustment 111,177 holdings remained in the dataset. These same holdings were also removed from the movements data which contained details of 959,335 movements prior to this adjustment and 936,204 movements following this adjustment.

Step 4- Adjusting the starting number of sheep at CPHs which have only movements away from the CPH and no movements of sheep into the CPH.

(i) Search across all the movements for departure CPHs which are also not destination CPHs

(ii) For each of these CPHs, add together the total number of sheep that move from that CPH in the year.

(iii) Minus this number from the number of sheep in the agricultural survey.

(iv) If the result is negative, then add the deficit back to the survey result.

Step 5- Adjusting the starting number of sheep at CPHs which have movements to and from the CPH.

(i) Calculate the cumulative measurement at time = n

(ii) Cumulative = cumulative at time = n-1 + movement at t = n

(iii) Find the minimum cumulative

(iv) Add this to the number of starting sheep at the CPH

(v) If the result is less than zero then minus the minimum cumulative from the starting number of sheep in the agricultural survey data (as this is a negative number it will add the difference).

There is a worked example of Step 5 on the next page.

Following these steps there were 37,191,725 sheep in the model; before the adjustments there had been 29,236,462, which is approximately a 27% increase in sheep after the adjustment. The impact the adjustment had on the mean number of sheep per farm is shown in Table 5.6.

Worked example of Step 5

Time	Movement	**Step 5i:** Change in sheep population at CPH1	**Step 5ii:** Cumulative to CPH1
1st April 2010	CPH1 – CPH2	-5	-5
23rd May 2010	CPH3- CPH1	+7	+2
5th September 2010	CPH1 – CPH3	-8	-6
17th December 2010	CPH2 – CPH1	-9	-15
19th December 2010	CPH4- CPH1	+20	+5

Step 5iii: The minimum cumulative from the Table is -15

Step 5iv: If the survey data shows that CPH1 has 10 sheep then 10 + - 15 = -5

Step 5v: Since the result to step iv is negative then minus thus number from the starting number 10 - - 5 = 15

If there are 15 sheep to start with in CPH1 then the number of sheep will never go negative.

Table 5.6 Number of farms and mean number of sheep per farm in each country in Great Britain according to the 2010 agricultural survey. The data provided are from after data cleaning Steps 1 to 3 (section 5.3.4.1) were applied and after the data were reconciled to the movement data (Steps 4 and 5, section 5.3.4.1).

Country	Number of Farms	Mean number of sheep per farm (After data cleaning Steps 1 to 3)	Mean number of sheep per farm (reconciled to movement data in Steps 4 and 5)
England	68282	213	280
Scotland	22023	313	404
Wales	20727	376	443
Unspecified country	145	143	163
Great Britain	111177	263	335

5.3.4.2 Determining which farms are neighbours

The distance_matrix() function in SimInf was used to calculate d_{ik} for each farm *i* and each of the neighbours *k* that were within 2km distance of *i*. All farms less than or equal to 2000m (2km) distance away from each other were considered to be important in transmission as described in Chapter 3.

The distance_matrix() function requires unique pairings of easting and northing. However, only 106480 holdings (of the 111,117 holdings used in the model, Table 5.6) had a distinct easting and northing and there were multiple holdings with the same easting and northing. These holdings may have had the same owner, who used the same easting and northing for all of the CPH numbers they own in an area. Alternatively, neighbouring farms may have used the same easting and northing as each other if they were using an approximation.

In order to ensure that each CPH had different easting and northings but were still close enough to be joined together in the distance matrix, the easting and northings within each group of replicates were adjusted slightly. Each collection of replicate easting and northings were numbered from 1 to the total number of replicates, then this number was added to both the easting and northing for that replicate. The first replicate in the list kept the original easting and northing.

As the coordinate referencing system is British National Grid, the numbers added would be metres. The maximum number of the same type of easting and northing was 110. This would make the 110th replicate be 155m away from the original holding and so it would still be within the within the 2000m (2km) used to select farms with the d_ik function. In addition, the 3rd quartile and mode of the number of CPHs within groups of replicates of eastings and northings was 2 and therefore, in most cases replicates within groups would only be ~2.83m away from each other, which would be captured within the 10m of higher transmission (explained in 5.3.3.2). Therefore, this method of adjusting replicate easting and northings is thought to be a good workaround for this issue.

5.3.4.3 Initial disease state sizes for holdings

The number of susceptible sheep in each holding was set to be equal to the number of sheep at the start of the simulation, as calculated in section 5.3.4.1. All other compartment sizes were set to zero, except for farms which were set to be initially infected with scab. The initially infected farms were selected based on the farms that were infected in December 1975 according to the MAFF data. It was assumed that all the farms reporting infection in December were still infected on the 1st January 1976 (the simulation start date). Data on infected farms in December 1975 were selected to initialise the model because this month almost three years post scab was re-introduced into Great Britain and before any national control programs had been implemented. From the end of 1972- 1976, regional control methods were used to try to control outbreaks of scab, but these were unsuccessful, and the disease became endemic (French et al., 1999). Therefore, initialising the model with these farms gives a good indication of the number and location of farms that were infected once scab became endemic and before any national control methods had been used.

Farms (n=47) that were identified as having an outbreak in December 1975 in the MAFF data were matched to the corresponding farms in the APHA data based on their easting and northing coordinates. This was achieved by identifying which farms were closest in distance between the two datasets, using a distance matrix in QGIS v 3.4. This identified a replicate farm which was removed. There were seven farms from the MAFF data that did not have specific coordinates or grid references for their geographical location. The county in which the farms was located was available for four of these cases and used to select a farm from the same county in the APHA data at random using the "sample_n" function from the "tidyverse" package (Wickham et al., 2019) in R. Once this data processing had been completed this left 44 farms. There were 11 holdings which had no sheep in their initial conditions and so there were only 33 farms that had infected sheep at the start of the simulation (Fig. 5.11). The number of infected sheep in each of those holdings was set to be equal to the total number of sheep in the holding. Across these 33 farms there were 6846 sheep and therefore this number of sheep were infected in total at the start of the simulation.

REDACTED FIGURE: SENSITIVE AND IDENTIFIABLE INFORMATION

Fig. 5.12 The farms initially infected in the model simulation. The red circles indicate the farms that were infected in January 1976 according to MAFF data and the black circles indicate the farms from the agricultural survey data that were identified to be geographically closest. There were four farms from the MAFF data that did not have specific coordinates or grid references for their geographical location, but the county in which the farms was located was available and so was used to select four farms at random from the corresponding counties in the agricultural survey data.

5.3.4.4 Dipping

It was decided to simulate a national dipping strategy in the autumn as this was the most common national scab treatment used between 1973-1992 (Table 5.2). Dipping was assumed to occur for a period of six weeks following the 23rd September (day 267- day 309 in the model) which are the timings which were usually used when implementing a national autumn dip (according to the Sheep Scab (National Dip) Order 1990). Each farm was randomly allocated a date in this period at which they would treat and then the treated sheep would be protected for a period of 60 days following the day of treatment. It was assumed that all sheep were treated within a holding when treatment occurred.

In the model, treatment is implemented for each farm as a scheduled event (as fully described by Widgren et al. 2019) and previously described for movement events in section 5.3.2.3.2. There were two data frames made; one specifying the treatment events and the other specifying the recovery from treatment events. In these data frames there was a row for each treatment event occurring at a farm (only one per farm in this simulation). The columns of these data frames are described in Table 5.7. (for the treatment events) and Table 5.8 (for the recovery events).

Table 5.7 Explanation of the data frame used to implement treatment as scheduled events in SimInf

Column name	event	time	node	dest	n	proportion	select	shift
Example	intTrans	269	1	0	0	1	2	1
Explanation	Type of event – here this is an internal transmission event because sheep are moved between disease states within farms	Day of model simulation that event happens	Node of interest (ID number)	If this was a movement event, the node ID of the destination.	The number of sheep moved. We use a proportion here so this remains at 0.	100% of sheep in this node are moved.	This refers to column 2 from the E matrix in the r code in the Appendix which specifies that the movement happens from compartments S, I and C	This refers to column 1 in the N matrix is in r code in the Appendix which specifies which compartment sheep in other compartments move to. Here they all move to the "treated" compartment

Table 5.8 Explanation of the data frame used to implement recovery from treatment as scheduled events in SimInf

Column name	event	time	node	dest	n	proportion	select	shift
Example	intTrans	269	1	0	0	1	3	2
Explanation	Type of event – here this is an internal transmission event because sheep are moved between disease states within farms	Day of model simulation that event happens	Node of interest (ID number)	If this was a movement event, the node ID of the destination.	The number of sheep moved. We use a proportion here so this remains at 0.	100% of sheep in this node are moved.	This refers to column 3 from the E matrix in the r code in the Appendix which specifies that the movement happens from compartment T	This refers to column 2 in the N matrix is in r code in the Appendix which specifies which compartment sheep in other compartments move to. Here they all move to the "susceptible" compartment

5.3.4.5 The settings used in the SICTDe_sp function

The SICTDe_sp function from the local adapted version of SimInf (code in the Appendix) was used to run the model, with u0 set with the initial compartment sizes as described in section 5.3.4.3. The events contained the movement events as described in section 5.3.2.3.2 and dipping events as described in 5.3.4.4 bound together as one data frame. The parameters were set at the values given in 5.3.3. The distance matrix used was as described in 5.3.4.2. The model was run for a period of 365 simulated days.

5.3.5 Approximate Bayesian Computation

Sequential Monte Carlo approximate Bayesian computation (SMC-ABC) was used to estimate the posterior distribution of three parameters; the daily contribution to environmental pressure per infected individual (α), the decay rate of the environmental infectious pressure (β) and the indirect transmission rate from the environmental compartment *j* to susceptible sheep in holding *i* (υ_j). The prior distributions used were as described in section 5.3.3.

The ABC_sequential() function from the R package "EasyABC" Jabot et al. (2015) was used with the Lenormand method, since this has been shown to be the most efficient method (Lenormand et al., 2013). The model summary statistics used were the daily incidence of scab across all holdings in the model in a one-year period and the yearly incidence. The targeted summary statistics were the average daily incidence across 1973 to 1992 as reported in the MAFF data (data fully described in Chapter 3) and the average yearly incidence (75 cases). There were 400 simulations, the stopping criterion ($Pacc_{min}$) was 0.11 and the proportion of particles kept at each step of the algorithm was 0.5.

From the 200 particles that remained after SMC-ABC, those that had a yearly incidence within the range of yearly incidence across from the reported data from 1973-1992 (minimum 18 cases per year, maximum 175 cases per year) were selected for the analysis (n = 161).

5.3.6 Exploring spatial patterns

Since long distance movements were included in the model here, it was hypothesised that the spatial spread of scab would be different to the spatial spread that was seen in the Chapter 3 model where it was only possible for disease to spread between farms via neighbours.

In order to test this, the model was run once under the conditions described in 5.3.4 and using the parameters given in Table 5.5. For the unknown parameters being estimated in the SMC-ABC (α, β and υ_j), 50 simulations of the SMC- ABC were run (but otherwise as described in 5.3.6) and the outputs that had a yearly incidence within the range of the yearly incidences in the MAFF data from 1973-1992 were selected. The mean values for each of the unknown parameters ((α, β and υ_j), from these selected outputs were used to parameterise the model. Farms that had sheep that were infected or carriers on day 365 of the simulation were identified and plotted using QGIS 3.4.

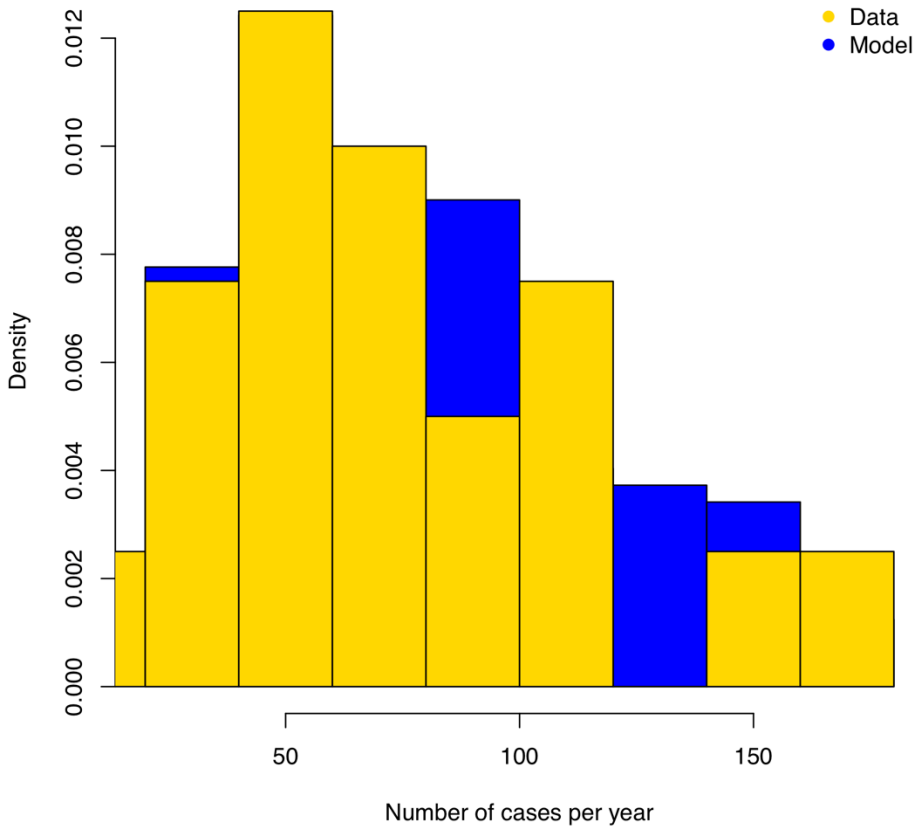
5.4 RESULTS

As parameterised, the SICTDe_sp model presented in this chapter appears to closely fit the reported MAFF data from 1973-1992, in both the yearly (Fig. 5.13) and the daily incidence (Fig. 5.14). The numbers of cases in the model output are consistently within the same order of magnitude as the data and the model output also shares a similar seasonal pattern to the data (Fig. 5.14). The seasonal patterns in the model output follow even more closely the patterns seen in the MAFF data when a national dip occurred in the autumn (Fig. 5.14b) (which is the same treatment strategy implemented in the model).

The estimated posterior distributions for υ_j, α and β give more of an indication of suitable parameter values than the prior distributions (Fig. 5.15- Fig.5.17 respectively), with mean values of $2.2\text{x}10^{-4}$, $4.1\text{x}10^{-3}$ and $4\text{x}10^{-2}$ respectively (respective prior mean values were approximately $3\text{x}10^{-4}$, $6\text{x}10^{-3}$ and $5\text{x}10^{-2}$).

The spatial distribution of infected holdings on day 365 of a simulation (described in section 5.3.7) is fairly dispersed, with some holdings within a close radius of a

holding which was initially infected on day 1 of the simulation (Fig. 5.18) and others which are far from any initially infected holding (for example, three holdings in Kent are approximately 155km away from the nearest holding that was infected on day 1 of the simulation).



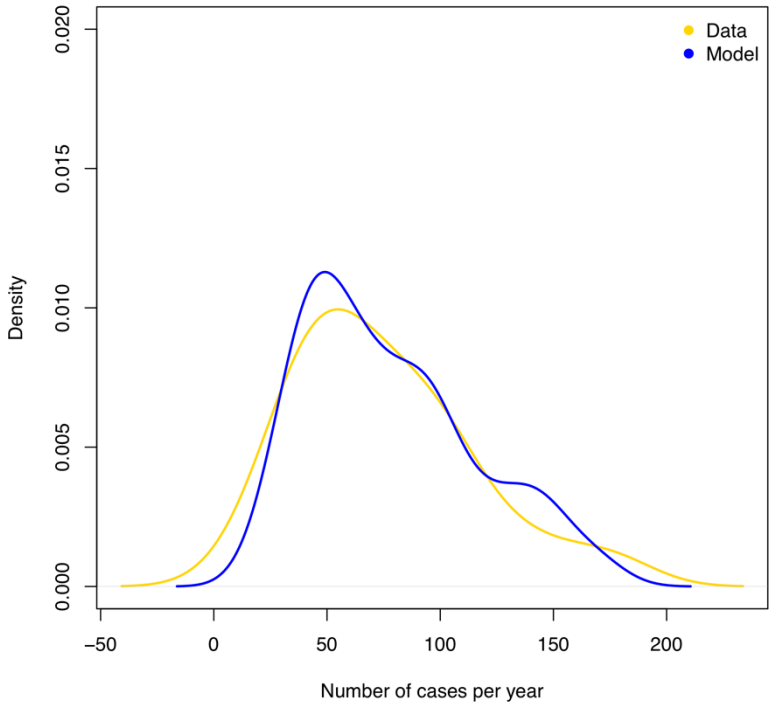


Figure 5.13 The density of the total number of cases of scab per year from the 1973-1992 MAFF data and from the best particles from the SMC-ABC (n=161) of the SICTDe_sp model.

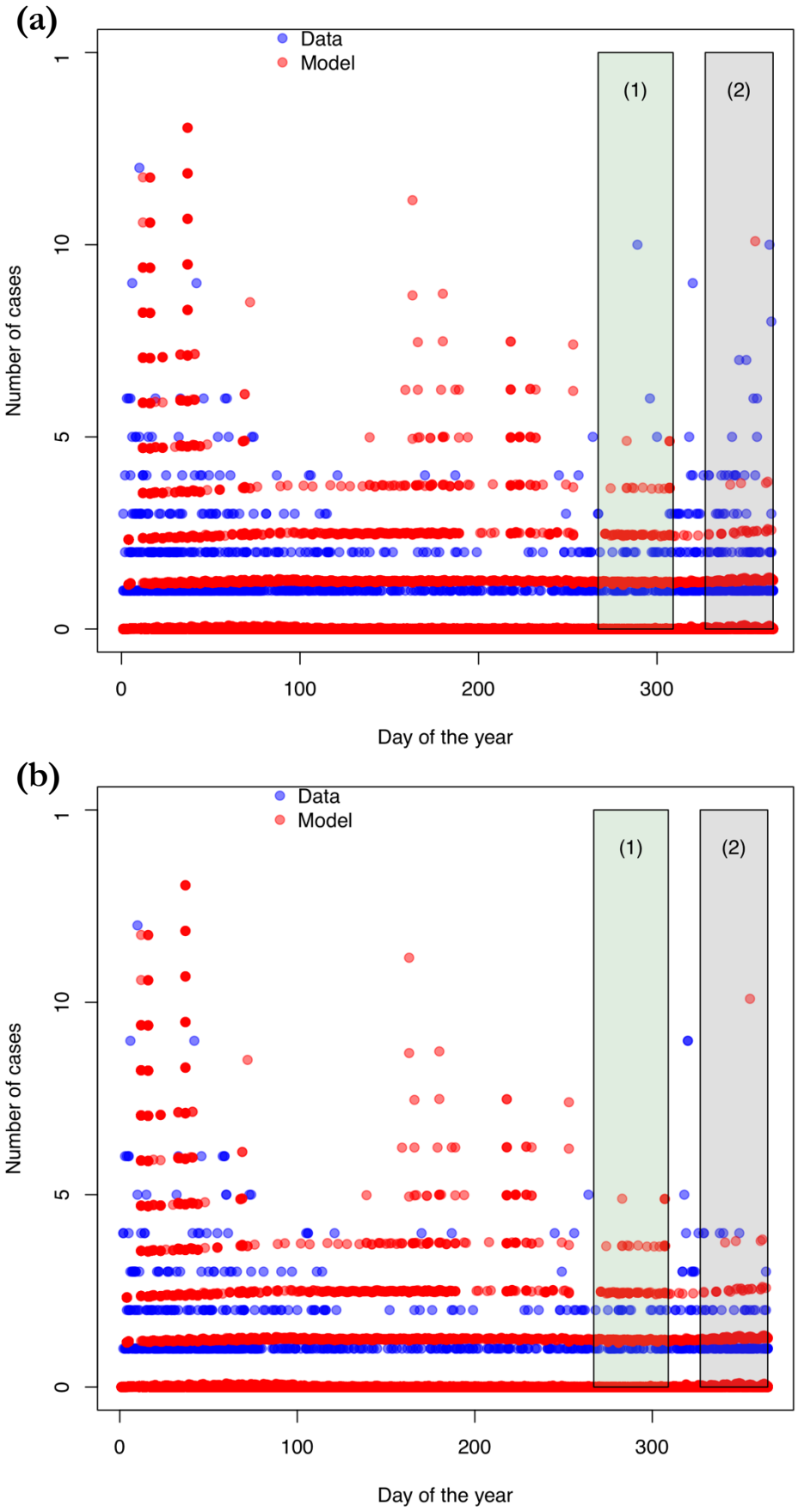


Fig. 5.14 The number of cases of scab each day in a one year period from years given in the MAFF data (blue) and from the best particles from SMC-ABC (n= 161, red) of the SICTDe_sp model. In the model, all sheep in each individual holding are dipped on a randomly selected day from day 267-309 ((1)- green rectangle) and sheep are protected from scab for 60 days post dip ((2)- grey rectangle showing when the protection is wearing off) **(a)** All years from the MAFF data were plotted **(b)** Only years where a national autumn dip was implemented were plotted.

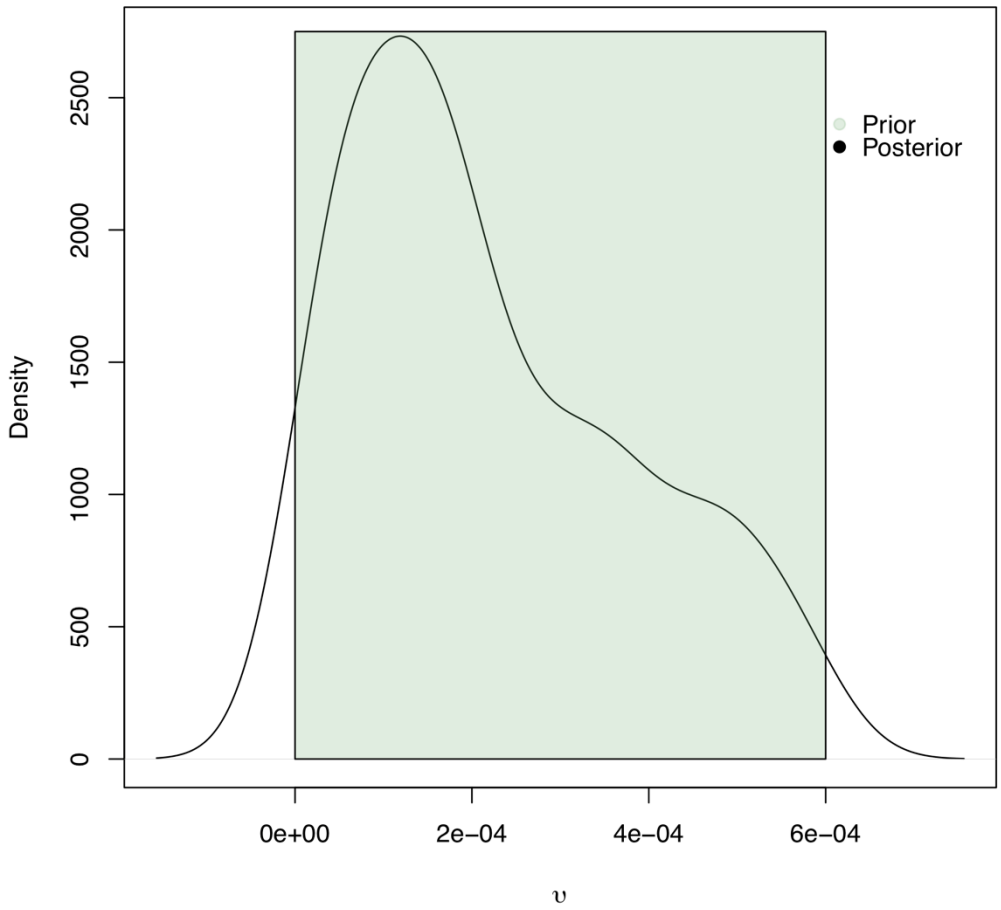


Fig. 5.15 The prior and estimated posterior distribution of υ_j (the indirect transmission rate from the environmental compartment j to susceptible sheep in holding i) given by the SMC-ABC algorithm.

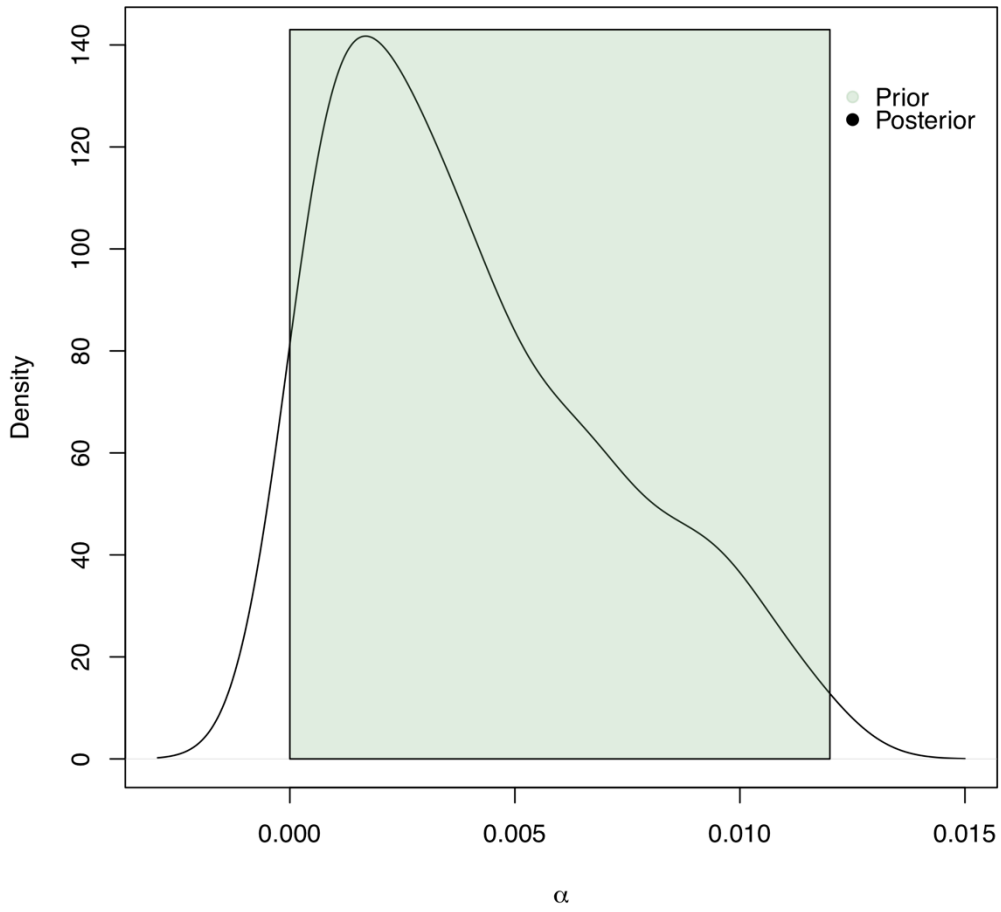


Fig. 5.16 The prior and estimated posterior distribution of α (the daily contribution to environmental pressure per infected individual) given by the SMC-ABC algorithm.

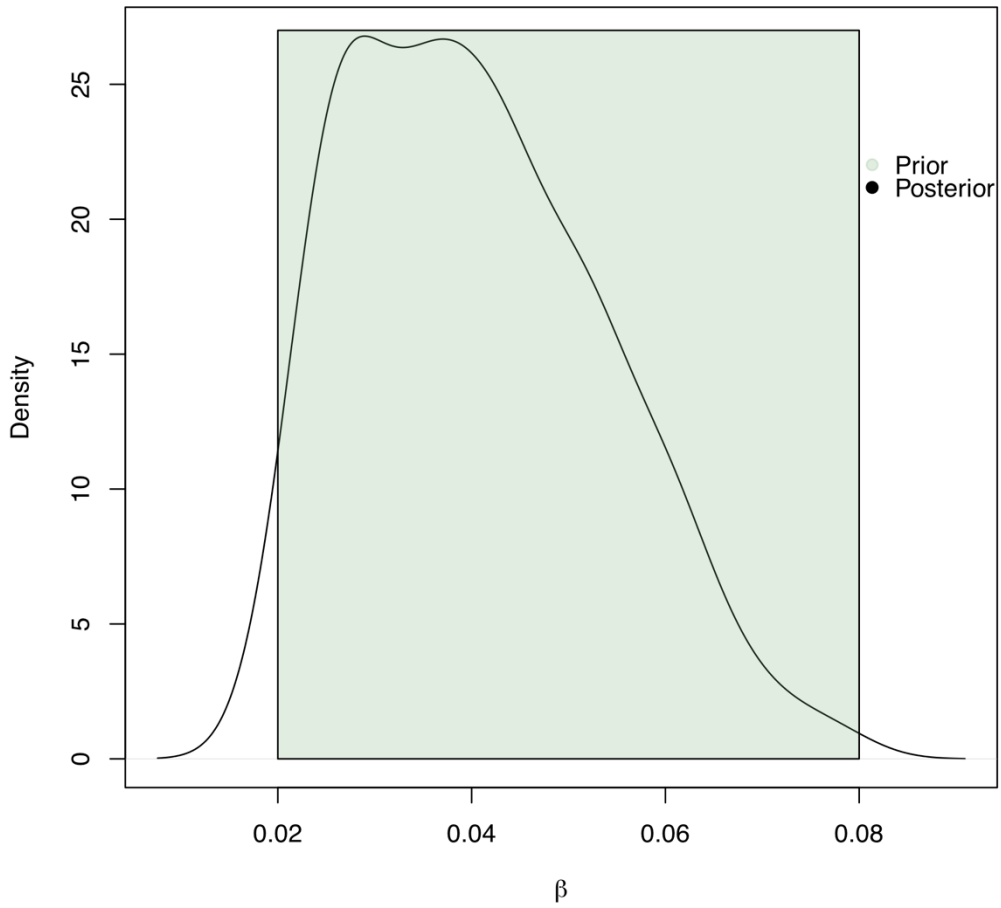


Fig. 5.17 The prior and estimated posterior distribution of (β) the decay rate of the environmental infectious pressure given by the SMC-ABC algorithm.

REDACTED FIGURE: SENSITIVE AND IDENTIFIABLE INFORMATION

Fig. 5.18 The locations of farms infected on day 1 (red circles) and day 365 (blue circles) of one simulation of the SICTDe_sp model (Described in section 5.3.7).

5.5 DISCUSSION

In this chapter, the within-flock transmission model from Chapter 4 is extended to include transmission between neighbouring sheep holdings and via long distance sheep movements. Sheep movement and agricultural survey data provided by DEFRA from 2010 are used to capture realistic movement patterns. The published data from French et al. (1999) described in Chapter 3 is re-analysed here to identify summary measures that can be used for model fitting. SMSC- ABC is then used to estimate three model parameters: the environmental pressure per infected individual (α), the decay rate of the environmental infectious pressure (β) and the indirect transmission rate from the environmental compartment *j* to susceptible sheep in holding *i* (υ_j). The fitted model is able to capture the number of farms infected in a year as well as seasonal patterns.

During the autumn dipping period in the model simulation (indicated by the boxes on Fig. 5.14), the model most closely matches the seasonal pattern seen in the years of the data when either an autumn or both a summer and autumn dip were used. More cases were seen in the data near the end of the year in the years when an autumn dip was not used (Fig. 5.1 and Fig. 5.14b). The model was fitted to data across all years in 1973-1992, yet the impact of the national autumn dip implemented in the model is still clearly visible in the model output. This suggests that the model will predict well the impact of different treatments used in future versions of the model. In addition, it also suggests that the known seasonal pattern of scab could largely be attributed to the timings of treatment strategies, which was also suggested by French et al. (1999). Other reasons for the seasonal variation relating to the biology of sheep or *P.ovis* mites in scab have previously been hypothesised (and fully described in section 1.5.1, Chapter 1 of this thesis), however, there is little evidence on the individual impact of these. The results presented here could provide new evidence on the importance of the timing and synchrony of scab treatment. Future versions of the model will explore the impact of different treatment strategies in more detail.

In the Chapter 3 model, disease transmitted from the initially infected farms through clusters of highly connected neighbouring farms and then was limited to the edge of these clusters. However, in the reported MAFF data, the spatial location of reported

cases appeared to be more dispersed from the location of the original introduction. It was inferred that this would be due to the fact that the Chapter 3 model did not contain long distance movements. The model in the current chapter does include long distance movements and when plotting the infected farms on the last day of the simulation (365) it does appear that farms are often spatially dispersed from the farms that were infected on day 1 of the simulation. There are certain farms infected on day 365, such as those in Kent, which are approximately 155km away from the nearest farm that was infected on day 1 of the simulation. This provides more evidence for the importance of long-distance movements of sheep in the transmission of sheep scab, which could have important implications in controlling the disease.

Further work could include running the SMC-ABC with more simulations than presented here and with a smaller stopping criterion. Lenormand et al. (2013) recommend that the stopping criterion is between 0.01 and 0.05 (with the proportion of particles kept at each step of the model between 0.3 and 0.7), while here the stopping criterion was 0.11. A few simulations of the model appear to slightly overestimate the number of cases seen in the middle of the year (Fig. 5.14) and the yearly incidence in the model is a slight overestimate of the data (Fig. 5.13). Therefore, it would be useful to see whether with more simulations and a lower stopping criterion whether or not these overestimations are only seen in outlier model outputs.

5.6 CONCLUSION

A metapopulation model of sheep scab transmission is presented here which is able to capture the number of farms infected in a year as well as seasonal patterns seen in the MAFF data from 1973-1992. The seasonal patterns in the model most closely match the years in the data when an autumn dip was used (which is the same treatment method used in the model simulations). This provides new evidence on the importance of the timing and synchrony of scab treatment. In addition, more evidence is given here for the importance of long-distance movements of sheep in the transmission of sheep scab.

Chapter 6

TREATMENT STRATEGIES FOR SHEEP SCAB: AN ECONOMIC MODEL OF FARMER BEHAVIOUR

This chapter forms the basis for a published paper:

Nixon, E., Rose Vineer, H. & Wall, R., 2017. Treatment strategies for sheep scab: An economic model of farmer behaviour. *Preventive Veterinary Medicine,* 137(A), pp. 43-51.

CONTRIBUTIONS TO THE PUBLISHED PAPER

Emily Nixon was the main researcher on this project and is the corresponding author; wrote the model, analysed the model results and wrote the manuscript

Hannah Rose Vineer contributed to the underlying study concept and critically reviewed the manuscript

Richard Wall supervised the project and critically reviewed the manuscript

SUMMARY

The unwillingness of farmers to use routine prophylactic treatment has been cited as a primary contribution to the growing incidence of sheep scab in the United Kingdom since the disease was deregulated in 1992. However, if farmers behave rationally from an economic perspective, the optimum strategy that they should adopt will depend on the risk of infection and the relative costs of prophylactic versus therapeutic treatment, plus potential losses. This calculation is also complicated by the fact that the risk of infection is increased if neighbours have scab and reduced if neighbours treat prophylactically. Hence, for any farmer, the risk of infection and optimum approach to treatment is also contingent on the behaviour of neighbours, particularly when common grazing is used. Here, the relative economic costs of different prophylactic treatment strategies are calculated for upland and lowland farmers and a game theory model is used to evaluate the relative costs for a farmer and their neighbour under different risk scenarios. The analysis shows that prophylaxis with organophosphate (OP) dipping is a cost-effective strategy, but only for upland farmers where the risk of infection is high. In all other circumstances prophylaxis is not cost effective relative to reliance on reactive (therapeutic) treatment. Hence, farmers adopting a reactive treatment policy only, are behaving in an economically rational manner. Prophylaxis and cooperation only become economically rational if the risk of scab infection is considerably higher than the current national average, or the cost of treatment is lower. Should policy makers wish to reduce the national prevalence of scab, economic incentives such as subsidising the cost of acaricides or rigorously applied financial penalties, would be required to make prophylactic treatment economically appealing to individual farmers. However, such options incur their own infrastructure and implementation costs for central government.

6.1 INTRODUCTION

In the previous two chapters of this thesis, the main focus was to develop models that could be used to simulate patterns of scab transmission and which could, in the future, be used to identify appropriate control strategies for scab. Although effectiveness, defined as a reduction in incidence, is certainly an important characteristic of a successful disease control strategy, considering the economics of control is also important if stakeholders are to be encouraged adopt them (Dijkuizen et al. 1997). This is particularly important for livestock diseases where livestock are business assets, that form a wider part of a country's trade network (Rojas, 2009).

In some cases, it may be more cost-effective to manage a disease to a low incidence rather than attempting to eradicate it completely, if the costs of complete elimination exceed the total economic damage caused by low incidences of the disease (McInerney, 1987) – although clearly cost calculations need to be balanced against animal welfare considerations. This phenomenon may relate to sheep scab, where the costs of having sheep scab in 2005 were estimated to be £0.8 million of the overall cost to the sheep industry per year, while the costs of prevention were estimated to be £7.5 million (Nieuwhof & Bishop, 2005). This discrepancy between the cost of scab and the cost of prevention is thought to be an important driver behind the decision made by the British government in 1992 to no longer enforce preventive treatment for scab (MAFF, 1992; ADAS, 2008).

Since this deregulation in 1992, many farmers have chosen to abandon preventive treatment. A randomised response survey in Wales (Cross et al., 2010) found that a primary reason for this is the cost of treatment and labour (selected as one of the top three reasons by 52.47% of farmers). However, economic cost is not the only reason why farmers choose to not use preventative treatment; concern about the negative impact of organophosphate insecticides on the health of sheep dip operators may also explain this choice (selected as one of the top three reasons by 50.77% of farmers). This unwillingness to routinely use preventive treatment for scab is thought to have contributed to the increase in sheep scab prevalence seen after 1992 (Bisdorff et al., 2006; Bisdorff & Wall, 2008). The question remains today as to whether the cost of scab still is less than the cost of prevention and, therefore, from an economic perspective, what treatment strategies farmers should take, if any, to prevent scab.

No further estimates of the costs of sheep scab have been published since the Nieuwhof and Bishop study in 2005, which included the losses from growth rate reduction in infected sheep (Kirkwood, 1980), the loss in birth weight (Sargison et al., 1995) and the cost of treating scab. Their cost estimates are likely to be an underestimate since they did not include the cost of treatment of the entire flock once a scab outbreak was detected, even though if an outbreak is confirmed, by law, the whole flock must be assumed to be infected and treated (MAFF, 1997). In addition, the costs of wool loss, reproductive losses, additional food costs, mortality, labour, subclinical disease and ineffective treatments were not included in their estimate.

The two main treatments used to treat and prevent scab are plunge dipping in Diazinon organophosphate (OP) and injecting endectocide macrocyclic lactones (MLs) (Bisdorff & Wall, 2008). The residual activity of these treatments provides protection from scab for a limited number of days; up to 63 days for an OP dip (Kirkwood & Quick, 1981) and 60 days for MLs (NOAH, 2017). However, resistance to the three MLs used in scab management (ivermectin, doramectin and moxidectin) has been reported recently in *P. ovis* mite populations from Wales and South West England (Doherty et al., 2018; Sturgess-Osborne et al., 2019). Therefore, the future costs and risks of scab may be greater, as the efficacy of MLs decreases.

When looking at the long-term cost-effectiveness of preventative treatment, the risk of infection must be included in the calculations. Since the prevalence varies across different areas of Great Britain, the risk of infection can be assumed to vary in a broadly similar manner. The most recent surveys suggest that scab prevalence is higher in the uplands of Great Britain than in the lowlands and this is thought to be due to the more frequent use of common grazing in the uplands (Rose & Wall, 2012). The uplands generally encompass Scotland (with average scab prevalence 7.1%), Wales (20.5%) and Northern England (14.1%), while the lowlands comprise Central England (3.3%), South West England (6.4%) and East England (5.9%) (Rose, 2011). Taking into account these differences in risk would be important when looking at the cost-effectiveness of control strategies for sheep scab.

The risk of contracting sheep scab has been shown to be highly dependent on the scab status of neighbours; if neighbouring farms have scab then the risk is greater and in upland farms this has been shown to increase the risk of scab infection by a

factor of 10 (Rose & Wall, 2012). On the other hand, farms with neighbours that use routine preventative treatment for scab will be at a lower risk of contracting it themselves and therefore have less need to also use preventative treatment. Hence, for any farmer, the risk of infection and optimum approach to treatment is contingent on the behaviour of neighbours, particularly when contact between flocks is likely, as when common grazing is used.

Farmers do not always have access to information about their neighbour's strategy or about the current costs and risks of scab to aid their decision-making process. However, modelling of the system incorporating information about the costs using the mathematical framework of game theory von Neumann and Morgenstern (1944), allows an optimum strategy for a farmer to be determined without requiring knowledge of the neighbour's strategy. Game theory is use of mathematical models, depicting two or more individuals (players), who must choose whether to cooperate in a particular scenario (game). It is assumed that all players will make the choice that maximises their personal payoff, that is, they are rational (Myerson, 1991). The individual does not know what the other player, in this case the neighbour, will decide to do, however, the other player's actions affect disease incidence and infection risk (Shim et al., 2012). Game theory in a human public health context has been used for a number of infectious diseases, for example rubella (Shim et al., 2009) and influenza (Galvani et al., 2007). In addition, it has been applied to epidemiological studies of animal health, for example toxoplasmosis in cats (Sykes & Rychtar, 2015).

6.2 AIMS

The work described in this chapter aimed to examine the economic implications of disease control in scab by developing and analysing a game theory model which looks at the relative costs and benefits of different preventative treatment choices made by an individual farmer in relation to the unknown treatment choices made by a neighbouring farmer.

6.3 METHODS

6.3.1 Model construction and assumptions

A deterministic Game Theory model was constructed in Microsoft® Excel (Microsoft Corporation, Redmond, WA, USA) to determine the optimum sheep scab control strategy (to treat or not treat prophylactically) for a farmer in relation to the behaviour of their closest neighbour. It is assumed that a farmer has only one neighbour and so the game involves two players, a farmer (known as Farmer) and their neighbour (Neighbour). Both players are assumed to be economically rational, that is, they are motivated solely by profit and not by any other factors. They simultaneously decide whether or not to treat their flocks prophylactically for sheep scab. Four scenarios of prophylactic treatment are possible: Farmer and Neighbour treat, Farmer treats and Neighbour does not, Neighbour treats and Farmer does not and neither treat. For all scenarios it is assumed that both Farmer and Neighbour have the same flock size and that, if they both treat, they will use the same form of treatment. In all scenarios, both Farmer and Neighbour apply a reactive, therapeutic treatment in the event of an infection (as required by law). Every run of the model generates eight costs, one for each farmer during the four possible prophylactic treatment scenarios (Table 6.1).

The cost to Farmer/Neighbour per year when both farmers treat prophylactically (*Ctt*) is the cost of prophylaxis per ewe (and her lambs) (*PC*) plus the product of the probability that a farmer's flock may get scab despite the fact that both farmers treat prophylactically (*Ptt*) and the costs and losses per ewe (and her lambs) incurred if the flock does get scab (*L*), all multiplied by the number of ewes in the flock (*Ne*).

$$Ctt = Ne \cdot (PC + (L \cdot Ptt) \quad 6.1.$$

The cost to Farmer/Neighbour per year when they do not treat prophylactically but the other player does (*Cntt*) is the product of the probability that the flock gets scab when they do not treat prophylactically but their Neighbour does (*Pntt*), the costs and losses per ewe (and her lambs) incurred if the flock does get scab (*L*) and the number of ewes in the flock (*Ne*).

$$Cntt = Ne \cdot L \cdot Pntt \qquad 6.2.$$

The cost to Farmer/Neighbour when they treat prophylactically but the other player does not (*Ctnt*) is the prophylaxis cost per ewe (and her lambs) (*PC*) plus the product of the probability that a farmer's flock will get scab when they treat prophylactically but their neighbour does not (*Ptnt*) and costs and losses per ewe (and her lambs) incurred if the flock does get scab (*L*), all multiplied by the number of ewes in the flock (*Ne*).

$$Ctnt = Ne \cdot (PC + (L \cdot Ptnt) \qquad 6.3.$$

The cost to Farmer/Neighbour when neither treats prophylactically (*Cntnt*) is the probability that a farmer's flock gets scab when neither has used prophylaxis (*Pntnt*), multiplied by the costs and losses per ewe (and her lambs) incurred if the flock does get scab (L) multiplied by the number of ewes in the flock (Ne).

$$Cntnt = Ne \cdot L \cdot Pntnt \qquad 6.4.$$

Table 6.1 Scenarios of a game theory model depicting the financial outcomes for two neighbouring farmers deciding whether or not to use prophylaxis for sheep scab. *C* represents the cost to a farmer; subscript "*t*" is treat and subscript "*nt*" is not treat (subscript on the left refers to Farmer's choice and subscript on the right, Neighbour's). The numbers in brackets refer to the corresponding equation number. The cost to the left of each column shows the loss for Farmer and the cost to the right shows the loss for Neighbour.

		Neighbour	
		Treat	**Not Treat**
Farmer	**Treat**	C_{tt} (6.1), C_{tt} (6.1)	C_{tnt} (6.3), C_{ntt} (6.2)
	Not Treat	C_{ntt} (6.2), C_{tnt} (6.3)	C_{ntnt} (6.2), C_{ntnt} (6.2)

6.3.2 Parameter estimation

6.3.2.1 Probability parameters

The four probability parameters (*Ptt, Pntt, Ptnt, Pntnt*) were estimated using equations 6.5-6.9 and data from published literature (Table 6.2). They were estimated for upland and lowland farms, when using an OP dip or ML injection, for all four scenarios in the model (Table 6.3). The equations for the probability parameters were formulated using a decision tree (Fig. 6.1) which maps the possible outcomes in which Farmer gets scab when different preventative treatment choices of Farmer and Neighbour are used. Farmer can get scab either from Neighbour (denoted as the probability of infection given Neighbour is infected Pr(I|NI)) or from other sources (probability of getting scab Pr(S)). It is assumed that Neighbour can only get scab from other sources, not from Farmer. The parameters in bold in equations 6.5-6.8 are those which relate to the probability of Neighbour getting scab. The full parameter names for the parameters in equations 6.5-6.8 are given in Table 6.2.

The probability that Farmer gets scab when Farmer and Neighbour treat (P_{tt}) is the probability of Outcome A plus the probability of Outcome E (Fig. 6.1):

$$P_{tt} = \underbrace{\boldsymbol{Pr}(\boldsymbol{S}|\boldsymbol{T}) \cdot (\Pr(S|T) + \Pr(NS|T) \,.\, \Pr(I|NI))}_{Outcome\ A} + \underbrace{\mathbf{Pr}(\boldsymbol{NS}|\boldsymbol{T}) \,.\, \Pr\,(S|T)}_{Outcome\ E} \quad 6.5.$$

The probability that Farmer gets scab when Farmer does not treat and Neighbour does treat (P_{ntt}) is the probability of Outcome C plus the probability of outcome G (Fig. 6.1):

$$P_{ntt} = \underbrace{\boldsymbol{Pr}(\boldsymbol{S}|\boldsymbol{T}) \cdot (Pr(S|NT) + Pr(NS|NT) \,.\, \Pr(I|NI))}_{Outcome\ C} + \underbrace{\mathbf{Pr}(\boldsymbol{NS}|\boldsymbol{T}) \,.\, \Pr\,(S|NT)}_{Outcome\ G} \quad 6.6.$$

The probability that Farmer gets scab when Farmer treats and Neighbour does not treat (P_{tnt}) is the probability of Outcome I plus the probability of Outcome M (Fig. 6.1):

$$P_{tnt} = \boldsymbol{Pr}(\boldsymbol{S}|\boldsymbol{NT}) \cdot (\Pr(S|T) + \Pr(NS|T) \,.\, \Pr(I|NI)) + \boldsymbol{Pr}(\boldsymbol{NS}|\boldsymbol{NT}) .\, \Pr\,(S|T) \qquad 6.7.$$

Outcome I Outcome M

The probability that Farmer gets scab when neither Farmer or Neighbour treat (P_{ntnt}) is the probability of Outcome K plus the probability of Outcome O (Fig. 6.1):

$$P_{ntnt} = \boldsymbol{Pr}(\boldsymbol{S}|\boldsymbol{NT}) \cdot (\Pr(S|NT) + \Pr(NS|NT) \,.\, \Pr(I|NI)) + \mathbf{Pr}(\boldsymbol{NS}|\boldsymbol{NT}) \,.\, \Pr\,(S|NT) \qquad 6.8.$$

Outcome K Outcome O

6.3.2.1.1 The probability of getting scab when using preventative treatment (Pr(S | T)

Scab transmission was considered to occur only during the autumn and winter months when clinical infections are most prevalent (French et al., 1999). This assumption was used to calculate the probability of getting scab during the autumn and winter months when using treatment to prevent scab (Pr(S | T)):

$$Pr\,(S|T) = (Y \cdot N \cdot R_i) + ((1 - Y \cdot N) \cdot R) \qquad 6.9.$$

Where Y is the proportion of the autumn and winter months protected, N is the number of times the treatment is applied, R_i is the risk of scab when prophylactic treatment is used and R is the baseline risk where farmers treat reactively (i.e. in response to an infestation) and forego prophylactic treatment.

Y is calculated using the residual activity of a treatment divided by the number of days in a year it is assumed that you are likely to get scab (the autumn and winter months, assumed to be 180 days).

The protection conferred by prophylactic treatment is transitory. Therefore, this equation takes into account the risk of scab when a flock are protected by the prophylactic treatment ($Y \cdot N \cdot R_i$) and the risk of scab during the rest of the autumn and winter when the prophylactic treatment is no longer having an effect$((1 - Y \cdot N) \cdot R)$, giving an overall risk of scab for this time period.

Data from the literature was used with equation 6.9 to calculate the value of *Pr(S|T)* for all four environments. The literature used to calculate *Pr(S|T)* as well as other probability parameters is given in Table 6.2. and the calculated values are given in Table 6.3. A worked example for calculating the probability of scab given treatment (Pr(S|T) when an organophosphate dip in the uplands is used is demonstrated here:

Y (the proportion of the autumn and winter months protected) is the residual activity divided by 180 (the number of days in a year assumed to be in autumn and winter). The residual activity of an organophosphate dip is 63 days (Kirkwood & Quick, 1981), therefore:

$$Y = \frac{63}{180}$$

N (the number of times treatment is applied) is assumed to be 1.

R_i (the risk of scab) is assumed to be 1 minus the efficacy of the treatment. The efficacy of organophosphate dips are 99.5% (Table 20, Milne et al, 2007) and so:

$$R_i = 1 - 0.995 = \frac{1}{200}$$

R (the baseline risk of scab) is assumed to be the same as the prevalence of scab. The uplands are assumed to be Scotland, Northern England and Wales and the average prevalence across these countries in the most recent survey (Rose 2011) was 13.9% (used as a proportion here at 0.139).

Substituting in these values into equation 6.9, gives the following:

$$Pr\ (S|T) = \left(\frac{63}{180} \cdot 1 \cdot \frac{1}{200}\right) + ((1 - \frac{63}{180} \cdot 1) \cdot 0.139)$$

$$P\,r(S|T) = 0.092$$

This is the value for upland dip given in Table 6.3

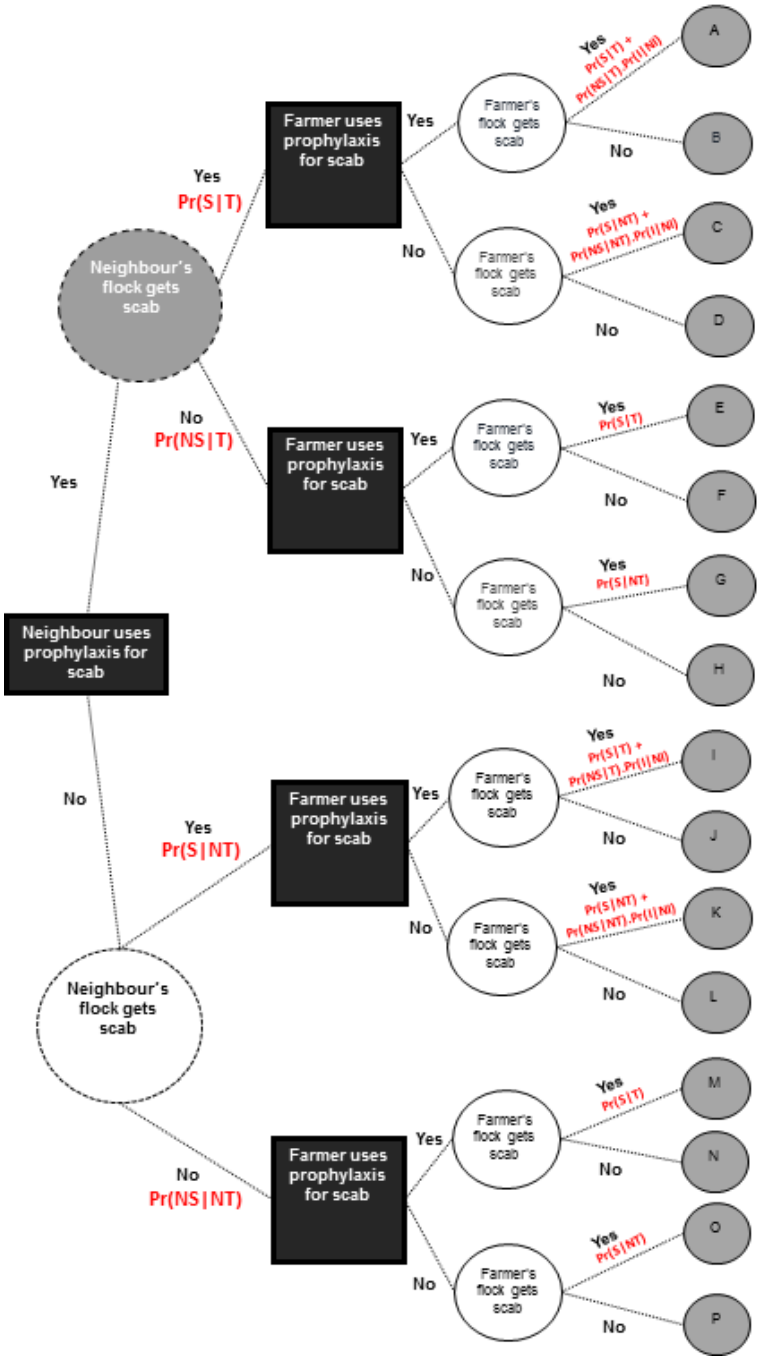


Fig. 6.1 The decisions (quadrilaterals) of two farmers (Farmer and Neighbour) choosing to use or not use prophylaxis for sheep scab, and the probabilities (writing in red) of different outcomes (circles) of these decisions in a game theory model. Probability values from Table 6.3 were assigned to the parameters depending on the model environment. The probability parameters from equations 6.1 to 6.4 were calculated as follows: *Ptt*- the probability of Outcome A + Outcome E, *Pntt*- the probability of Outcome C + Outcome G, *Ptnt*- the probability of Outcome I + Outcome M and *Pntnt*-the probability of Outcome K + Outcome O. To find the probability of each final Outcome (light grey circles), the probabilities (in red) of each branch leading to the required Outcome must be multiplied together. For each outcome where Farmer's flock do get scab, subtracting the probability of this outcome from 1 will give the probability of the matched Outcome where Farmer's flock does not get scab. Decisions made by both parties occur simultaneously.

Table 6.2 Parameters and the data sources used to calculate their values in equations 6.5-6.8 of a game theory model depicting the financial outcomes for two neighbouring farmers deciding whether or not to use prophylaxis against sheep scab.

Probabilities	Shorthand	Sources and calculations
Pr(scab | treatment)	Pr(S|T)	Equation 6.9, using the assumed probability of losses being prevented by application of organophosphate dip (99.5%, Table 20, (Milne et al., 2007) and residual activity (63 days, (Kirkwood & Quick, 1981)). Also, the residual activity of 1 injection of Cydectin 2% LA (60 days, (NOAH, 2017)) and efficacy (98.1% calculated efficacy at 54 days (closest to 60), in Table 3 (incidence), (Astiz et al., 2011). Y in equation 6.9 is calculated using the residual activity divided by 180 (the number of days assumed to be in the autumn and winter months). R_i in equation 6.9 is calculated by subtracting the efficacy of treatment from 1. Here, it is assumed that the treatment is only applied once a year (N=1). Baseline risk was the same as the prevalence (Pr(scab | no treatment)
Pr(no scab | treatment)	Pr(NS|T)	1- Pr(scab | treatment)
Pr(scab | no treatment)	Pr(S|NT)	Upland prevalence was the average prevalence of Scotland, Northern England and Wales. Lowland was average of Central, East and South West England (Rose, 2011))
Pr(no scab | no treatment)	Pr(NS|NT)	1-Pr(scab | no Treatment)
Pr(infection | neighbour infected)	Pr(I|NI)	Calculated using the odds ratio for neighbours with scab from Table 2 in Rose & Wall (2012) for upland (Probability= odds ratio/ (1+odds ratio)). Estimated for lowland based on evidence from Rose & Wall (2012)
Pr(healthy| neighbour infected)	Pr(H|NI)	1-Pr(infection | neighbour infected)

Table 6.3 Probability of possible outcomes in a game theory model where a famer and their neighbour are deciding whether to use preventative treatment for sheep scab. These values were estimated using data from the literature as shown in Table 6.2 and were used along with equations 6.5-6.9 to estimate the values of the probability parameters in the model.

Probability	**Dip**		**Inject**	
	Upland	**Lowland**	**Upland**	**Lowland**
Pr(scab | treatment)	0.092	0.036	0.099	0.041
Pr(no scab | treatment)	0.908	0.964	0.901	0.959
Pr(scab | no treatment)	0.139	0.052	0.139	0.052
Pr(no scab | no treatment)	0.861	0.948	0.861	0.948
Pr(infection | neighbour infected)	0.91	0.2	0.91	0.2
Pr(healthy | neighbour infected)	0.09	0.8	0.09	0.8

6.3.3 Costs of treatment and losses

Two treatments were considered here: an OP plunge dip with residual activity of 63 days and a long-acting injectable formulation using a macrocyclic lactone (ML) with a residual activity of 60 days. Both could be used either as a prophylactic or a therapeutic treatment of infection. There was considered to be no difference in the cost of the product when used as a prophylactic or a therapeutic treatment, as the dosage will not differ in either case; product costs were obtained from veterinary wholesalers and dose rates were based on the manufacturer's guidelines (NOAH, 2010; NOAH, 2017). Flock costs were calculated for lowland and upland flocks based on the different lambing percentages. The costs of treatment included the cost of product and labour costs (Sewell et al., 1999; ADAS, 2013; Nix, 2016). Dipping required the added costs of the certificate of competence (assumed to be spread over 10 years divided by the number of ewes to give a cost per ewe) plus dip disposal costs (ADAS, 2008; Myerscough College, 2014). The costs of installing and maintaining dipping facilities was not included in the calculation. At the point of treatment, the weight of all ewes was assumed to be 50 kg and lambs 30 kg (English Beef and Lamb Executive- EBLEX, 2014).

Losses resulting from scab infection were calculated for lowland and upland flocks as the sum of wool productivity loss, loss in lamb sales per ewe, additional feed costs for finishing lambs per ewe, losses due to scab-induced mortality and any therapeutic treatments applied (Table 6.5). Extra feed costs for finishing lambs assumed that the average weight of lambs at sale was 38 kg (EBLEX, 2014). It was anticipated that infected lambs, cull ewes and rams would be treated and most would make a full recovery, hence a low mortality rate of 0.002 per year was assumed for infected animals. If a flock was infected, then all individuals in the flock were assumed to be infected. There will be some heterogeneity in the severity of infection between individuals but the losses in wool and reproductive rate used in the model are average values and therefore the average was applied to all individuals in the flock. If a flock was not infected, then it was assumed that no individual within the flock was infected and no losses would occur. It was assumed that flocks could only become infected once per year.

Table 6.4 Estimation of prevention costs for sheep scab by injection of a long-acting macrocyclic lactone or an organophosphate dip. Cost of certificate of competence is a one-off payment assumed to be valid for 10 years.

Costs of prevention	Lowland	Upland	
Injecting	Cost (£)	Cost (£)	Sources
Cost of long-acting ML injection per ewe (+ lambs)	£1.42	£1.37	(NOAH, 2017)
Labour per ewe (+ lambs)	£0.40	£0.40	(ADAS, 2013)
Total cost of injecting per ewe (+ lambs)	£1.82	£1.77	-
Dipping	-	-	-
Cost of OP dipping product per ewe (+ lambs)	£0.39	£0.39	(NOAH, 2010)
Labour per ewe (+ lambs)	£0.86	£0.83	(Sewell et al., 1999); (Nix, 2016)
Cost of certificate of competence per ewe (+ lambs)	£0.01	£0.01	(Myerscough College, 2014)
Dip disposal costs per ewe (+ lambs)	£0.10	£0.11	Appendix 3, (ADAS, 2008)
Total cost of dipping per ewe (+ lambs)	£1.36	£1.34	-

Table 6.5 Costs of sheep scab infestation for lowland and upland farms in the UK

Costs of sheep scab	No scab		Scab		Losses due to scab		Source
	Lowland	Upland	Lowland	Upland	Lowland	Upland	
Wool sales per ewe	£2.40	£1.90	£1.57	£1.24	£0.83	£0.66	(Nix, 2016); (Rehbein et al., 2000b)
Lambing ratio	1.7	1.6	1.29	1.2	n/a	n/a	(Fthenakis et al., 2000); (Nix, 2016)
Lamb sales per ewe	£114.72	£99.20	£86.04	£74.40	£28.68	£24.80	(Fthenakis et al., 2000); (Nix, 2016)
Finishing food costs:	-	-	-	-	-	-	(EBLEX, 2014); (Hindson, 2002); (Kirkwood, 1980); (National Animal Disease Information Service, 2015); (Rehbein et al., 2000a)
- per lamb	£25.09	£23.01	£32.58	£29.88	£7.49	£6.79	
- for lambs per scabby ewe	-	-	-	-	£9.67	£8.15	
Lamb mortality costs per ewe	£0	£0	£0.17	£0.15	£0.17	£0.15	(Nix, 2016)
Cull ewe and ram mortality costs	£0	£0	£0.03	£0.02	£0.03	£0.02	(Nix, 2016)
Treatment:	-	-	-	-	-	-	Table 6.4
- injection per scabby ewe (+ lambs)	£0	£0	£1.82	£1.77	£1.64	£1.60	
- dip per ewe (+ lambs)	£0	£0	£1.37	£1.34	£1.25	£1.23	
Total loss per ewe (+ lambs)	-	-	-	-	-	-	
Injecting	-	-	-	-	**£41.02**	**£35.38**	
Dipping	-	-	-	-	**£40.63**	**£35.01**	

6.3.4 Model outcomes

The model was parameterised for four environments: a lowland flock treating prophylactically with a long-acting ML injection, a lowland flock treating prophylactically with an OP dip, an upland flock treating prophylactically with a long-acting ML and an upland flock treating prophylactically with an OP dip. It was assumed that the number of ewes in each flock (N_e) was equal to 500. Within these four environments the four prophylactic treatment scenarios described in section 6.3.1 and given in equations 6.1-6.4 were run. The output of the model gave the losses in GBP (£) for Farmer and Neighbour. Each model run summed the costs for each player over a one-year period.

The model identified the optimum strategy which minimised costs/losses, in each of the four prophylactic treatment scenarios (equations 6.1–6.4) within each environment. If the cost to Farmer when both Farmer and Neighbour treated prophylactically was greater than the cost to Farmer when only Neighbour treated prophylactically (Ctt > Cntt) then the optimum strategy was to not treat prophylactically. If the cost to Farmer when only they treated prophylactically was greater than the cost when neither Farmer or Neighbour treated prophylactically (Ctnt > Cntnt) then the strategy was to not treat prophylactically, otherwise the optimum strategy was to treat prophylactically. If both Ctt > Cntt and Ctnt > Cntnt, or Ctt < Cntt and Ctnt < Cntnt (i.e. had the same optimum strategy), then the overall strategy was described as strictly dominant. However, if two different strategies emerged (e.g. Ctt < Cntt and Ctnt > Cntnt) then there was no dominant strategy. The optimum strategy for the Neighbour was calculated in the same way.

Once the optimum strategy had been found one-at-a-time (OAT) sensitivity analyses were undertaken on three parameters to identify how variation on their values affected the optimum strategy: baseline scab risk, overall prevention cost and the cost of the prophylactic treatment product alone. Baseline risk was varied from 0 to 0.5 (0% risk of scab to 50%) at 0.005 intervals. Overall prevention cost per ewe and her lambs was varied from £0 to £2 at intervals of £0.05. The cost of the prophylactic treatment product per ewe and her lambs was also varied from 0 to £2 at intervals of £0.05.

6.4 RESULTS

6.4.1 Farming system

The average cost per annum of having sheep scab in a lowland flock was calculated as £40.84 per ewe and her lambs (range £40.63–£41.02, Table 6.5) and £35.12 per ewe and her lambs in an upland flock (range £35.01–£35.38, Table 6.5). The minimum output per ewe (and her lambs) has been estimated to be £59.20 for lowland flocks and £48.30 for upland flocks (Nix, 2016). Prophylaxis is less expensive for upland flocks than for lowland since upland ewes have a lower lambing percentage. It is less expensive to use an OP dip for prophylaxis as opposed to injection of MLs for both upland and lowland flocks (Table 6.4).

For lowland farmers using a long-acting ML injection prophylactically there is a strictly dominant strategy not to use prophylaxis, as it costs more for Farmer in the prophylaxis scenarios (Farmer treats prophylactically and Neighbour does not, or both treat) than in the scenarios where Farmer does not use prophylaxis (Neighbour treats and Farmer does not, or neither treats) (Table 6.6d). Choosing not to treat prophylactically prevents a loss of £687 for Farmer if Neighbour treats and £688 if Neighbour does not treat. The same applies to treating prophylactically with an OP dip on a lowland farm, which costs an additional £353 per annum when Neighbour treats and £354 if Neighbour does not treat (Table 6.6c). Co-operation (both treat) using an ML would result in a loss of £644 each for Farmer and Neighbour and £289 each when using a dip.

For upland farmers who use an ML, there is also a strictly dominant strategy not to use prophylaxis (Table 6.6b). Prophylaxis would cost an extra £242 per annum for Farmer if Neighbour also uses prophylaxis and £268 if Neighbour does not. If both use prophylaxis, cooperation would prevent a loss of £312 for both Farmer and Neighbour. However, the strictly dominant strategy is still not to use prophylaxis as, regardless of Neighbour's strategy, Farmer always loses less by not treating prophylactically. In contrast, for upland farmers who treat using an OP dip, prophylaxis is a strictly dominant strategy (Table 6.6a), since Farmer always loses less money overall by using prophylaxis; £84 per annum if Neighbour also uses prophylaxis and £49 if he/she does not. If Neighbour and Farmer were to cooperate

(both use prophylaxis) they would each prevent a loss of £727 compared to a scenario where neither player uses prophylaxis.

Table 6.1 Game theory matrixes for four runs of a game theory model giving the costs (£) to two players (Farmer and Neighbour) when the players are deciding whether or not to use prophylactic treatment for sheep scab . (a) Two farmers in the uplands of Great Britain (Scotland, Northern England and Wales) and their individual decisions to use an organophosphate dip as prophylaxis for sheep scab **(b)** Upland farmers and Cydectin 2% LA injection **(c)** Lowland (Central, East and South West England) and dip **(d)** Lowland and injection. The numbers given are the cost in GBP (£) per annum and were generated in a game theory model built in Excel ®, using data available in the literature (Table 6.5). This included an average baseline risk of scab in the uplands of 13.9% (Rose, 2011). A 500 ewe flock was assumed. In each cell, the value on the left is the loss for Farmer and those on the right are Neighbour's losses. It is assumed that both farmers, if

(a)

		Neighbour	
		Treat	**Not Treat**
Farmer	**Treat**	3611, 3611	4289, 3695
	Not Treat	3695, 4289	4338, 4338

(b)

		Neighbour	
		Treat	**Not Treat**
Farmer	**Treat**	4072, 4072	4652, 3830
	Not Treat	3830, 4652	4384, 4384

(c)

		Neighbour	
		Treat	**Not Treat**
Farmer	**Treat**	1546, 1546	1611, 1193
	Not Treat	1193, 1611	1257, 1257

(d)

		Neighbour	
		Treat	**Not Treat**
Farmer	**Treat**	1913, 1913	1957, 1226
	Not Treat	1226, 1957	1269, 1269

6.4.2 Sensitivity analysis

For lowland farmers (both Farmer and Neighbour) using a long-acting ML injection there is a strictly dominant strategy to use prophylaxis only when scab prevalence is greater than or equal to 16% or to use an OP dip at a prevalence of greater than or equal to 10.5% (Fig. 6.2). For upland farmers using a long-acting ML injection there is a strictly dominant strategy to use prophylaxis when scab prevalence is greater than or equal to 20.5% or to use an OP dip when the prevalence greater than or equal to 13% (Fig. 6.2).

For lowland farmers, the strictly dominant strategy not to use prophylaxis is unaffected by the cost of the product at the range of treatment costs examined (Fig. 6.3b). However, reducing the overall prevention cost (treatment plus labour) did make it economically viable to use prophylaxis in the lowlands when this was equal to or below £0.70 (dipping) or £0.45 (injecting) (Fig. 6.3a). For upland farmers, varying the treatment product cost alone was enough to change the strategy, and a strategy of prophylaxis became strictly dominant when product costs were less than or equal to £0.50 (dip) or £0.85 (inject) per ewe and her lambs (Fig. 6.3b).

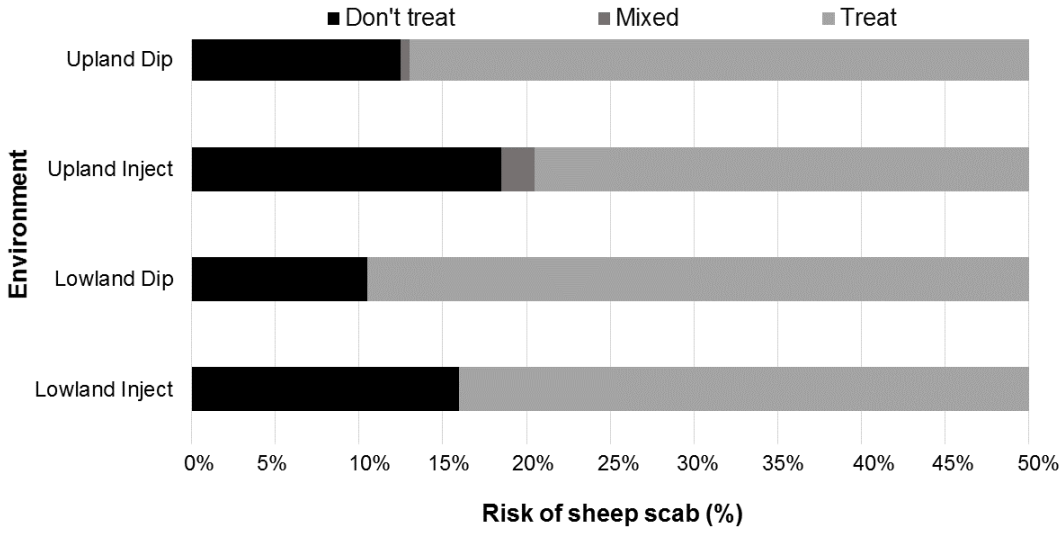
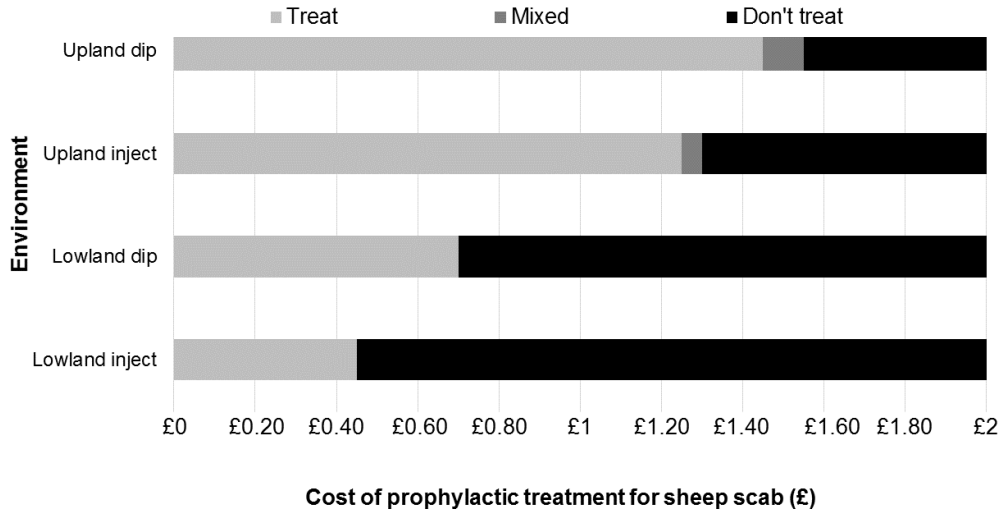


Fig. 6.2 The change in dominant treatment strategy for upland or lowland flocks exposed to different risks of sheep scab as predicted by sensitivity analysis using a game theory model. Dark bar – Farmer should not use prophylaxis for scab; mid-grey – no dominant strategy (mixed); light grey – Farmer should use prophylaxis for scab.

(a)



(b)

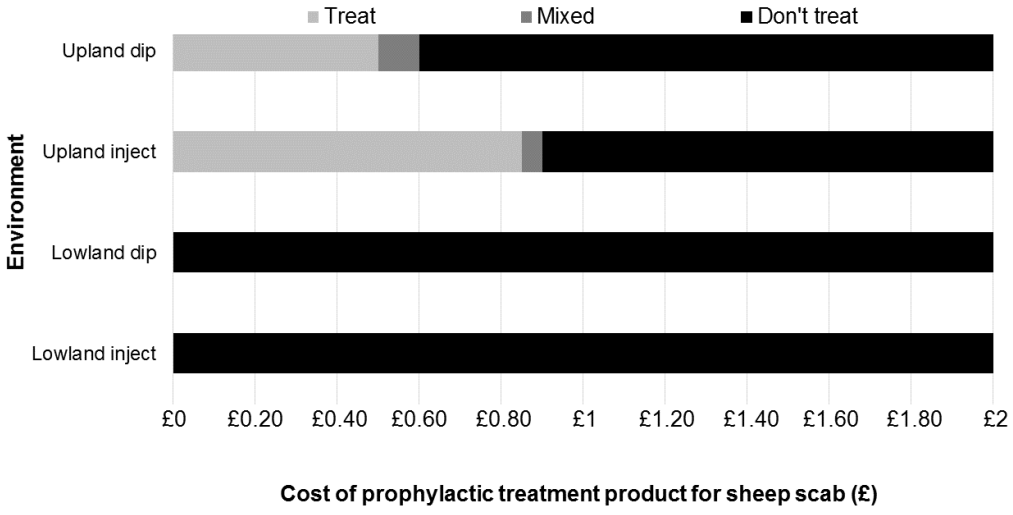


Fig. 6.3 The change in dominant treatment strategy for sheep scab for upland or lowland flocks in relation to variation in (a) aggregate prevention costs and (b) cost of prophylactic treatment product only, as predicted by sensitivity analysis using a game theory model. Dark bar – Farmer should not use prophylaxis for sheep scab; mid-grey – no dominant strategy (mixed); light grey – Farmer should use prophylaxis for sheep scab

6.5 DISCUSSION

Game theory recommends or explains decisions of individuals that are affected by and have implications for the decisions of others (Nash, 1951). It has been used previously to inform disease management, for example in salmon farming (Murray, 2014) and in the use of antibiotics (Porco et al., 2012). The Game Theory model developed here, based on data available in the literature, has been used to identify optimum economic strategies (to treat or not treat prophylactically for scab) in relation to the unknown strategy of a neighbouring sheep farmer. The model developed utilises all available data on the control and disease costs of scab, taking into account factors such as extra finishing costs and lower reproductive rates which have not always been included in previous estimates (Scott et al., 2007).

Not applying prophylactic treatment is a strictly dominant strategy if treating prophylactically with an ML injection on upland farms or with a ML or OP dip on lowland farms. This is because prophylactic treatment costs are high relative to the risks of infection. The only situation where prophylactic treatment was a strictly dominant strategy was for upland farmers using OP dip. However, the savings farmers might make compared with a scenario of no prophylactic treatment through prophylaxis are low (in a 500 ewe flock this was £84 per year or £49 per year depending on whether the neighbour does or does not use prophylaxis) and therefore in practice upland farmers may still choose not to use prophylaxis. It should also be noted that the costs of dipping infrastructure were not included in the calculation presented here and for farmers where such facilities are unavailable, the capital costs needed for their construction would again make prophylactic dipping uneconomic.

Cooperation (both farmers using prophylaxis) in upland farms always results in a lower mean loss per farmer (Table 6.6a & b). However, from a Game Theory perspective, there is still a strictly dominant strategy to not treat prophylactically if the treatment is by injection (Table 6.6b). This situation emulates the most common Game Theory example, the Prisoner's Dilemma (Axelrod & Hamilton, 1981). In both games, no players have an incentive to deviate from their strategy of non-cooperation and so, if we assume rationality, they will never choose to cooperate. It

has already been suggested that a lack of compliance by certain farmers during the compulsory dipping period of 1972–1992 was a key reason for the failure to eradicate sheep scab during this time and for its subsequent spread (Rose, 2011). The findings reported here suggest that non-cooperation is an economically rational response, as also suggested by Milne et al., (2007). Hence, if future control programs require compliance by all farmers, economic incentives or penalties would be required to encourage farmers to deviate from their most economically rational strategy.

Cooperation was still less favoured in lowland farms under current scab prevalence since there was a strictly dominant strategy not to use prophylaxis. In fact, if both Farmer and Neighbour co-operated in treating prophylactically the mean loss would be greater than if neither cooperated (Table 6.6c & d). Existing economic data also supports the idea that it is not always economically viable to use prophylaxis. For example, in Scotland in 2006, £5.1 million was spent on prophylaxis while losses due to scab were estimated to cost only £0.6 million (ADAS, 2008) (although the estimate of losses did not take into account all the costs, for example reproductive losses).

Although, given the most current average national prevalence values for scab (13.9% upland and 5.2% lowland, (Rose, 2011)), the current strictly dominant strategy is to only use prophylaxis if using an OP dip on an upland farm, the sensitivity analysis demonstrates that as the risk of scab increases this strategy changes. The prophylactic use of ML injections on upland farms becomes a strictly dominant strategy when the prevalence is above or equal to 20.5% and in lowland farms when the prevalence is above or equal to 16% (Fig. 6.2). Dipping on lowland farms becomes strictly dominant when the prevalence is above 10.5% (Fig. 6.2), with the difference between treatment types being attributed to lower cost of dipping based on a flock of 500 ewes. These results suggest that higher prevalence regional hotspots, with higher than average prevalence, could be good targets for prophylaxis programs. For example, in Wales, the prevalence has been reported to be above average at 20.5% (Rose, 2011) and at 35% (Cross et al., 2010) and therefore not only dipping, but also injecting with a long-acting ML at current costs-per-dose (Table 6.4) would be a cost-effective strategy in controlling sheep scab. If other higher prevalence regional hotspots can be identified (in either uplands or lowlands) prophylaxis might also be an optimum

strategy in these areas. Although, of course such targeted programmes bring with them additional management, surveillance and infrastructure costs that must be borne by central government of distributed between individual farmers in the area.

The prevalence estimates used in our study were based on a survey of around 400 sheep farmers in 2008 (Rose, 2011) and were found to be similar to those from a previous survey (Bisdorff et al., 2006). Although not completely up to date, these prevalence figures give a good representation of what current scab risks are likely to be in different regions in Great Britain. Unfortunately, they are only able to give prevalence estimates at a relatively crude regional scale which limits the identification of hotspots, although spatial models, such as the one presented in Chapter 3, may aid the identification of particularly high-risk regions. Furthermore, prevalence can be underestimated since farmers are often reluctant to admit to the presence of scab in their flocks (Cross et al., 2010) or may not report outbreaks if scab is a persistent problem within their flock or area. However, this could be overcome by the use of the Randomised Response Technique, a method which protects the farmers' anonymity and appeared to result in higher estimates of prevalence when employed in a survey by Cross et al., (2010) than found in previous surveys. In order to collect continuous prevalence data, media reporting methods such as the use of mobile phone applications could be used, as discussed by Walker, (2013). More detailed data on scab prevalence in certain regions would enable our model to inform farmers more accurately about whether and how they should be treating.

The sensitivity analysis of the cost of the prophylactic treatment product demonstrated that subsidising this cost alone was not enough to incentivise lowland farmers to use prophylaxis (Fig. 6.3b) and that the overall prevention cost (product cost plus labour costs, dip disposal costs etc., see Table 6.4) would need to be less than or equal to £0.70 (dip) or £0.45 (inject) per ewe (+ lambs) for prophylaxis to be economically viable for lowland farmers (Fig. 6.3a), based on projections for ewe output for 2016 (Nix, 2016). Although dipping may be economically viable in the uplands without subsidy, there have been concerns relating to its potential harmful effects to the environment and the operator, which may prevent certain farmers from choosing this method of treatment (Sargison et al, 2007). Subsidising the cost of ML product per ewe (+ lambs) to £0.85 or less would make it economically viable for

upland farmers to treat with injectable MLs as an alternative (Fig. 6.3b), based on projections for ewe output for 2016 (Nix, 2016). Alternatively, rigorously applied financial penalties would have the same economic effect.

Whether government would subsidise or otherwise incentivise preventative treatment enters the realm of balancing political against economic imperatives: clearly centralised management would bring a range of associated costs. These would include start-up, fixed or overhead costs (Tisdell, 2009) which could include further research costs, costs for contract negotiations, disease surveillance costs and costs relating to the monitoring of compliance and uptake (Rushton & Leonard, 2009). All of these factors would need to be considered in a cost-benefit analysis as described by Tisdell, (2009) before instigation of such a program. There has been debate in recent years as to whether animal health should be seen as a public or a private good and consequently whether the government should have a role in providing this service (Rushton & Leonard, 2009).

One significant problem with the modelling approach used here is that it assumes that farmers are strictly rational decision makers driven by economic concerns. In reality, however, the control of disease takes place within the entire-farm context and farmers have other goals, values and influences which also affect their decision-making processes, such as job satisfaction, peer pressure, animal welfare, farm succession, maintaining a way of life, stressful circumstances, personality and attitude to risk (Wallace & Moss, 2002; Long, 2013). When deciding which treatment to use for scab, farmers may be concerned about the impact of OP dips on the safety of their workers (Murray et al., 1992; Stephens et al., 1995; Fletcher & MacLehose, 2005; Sargison et al., 2007; Solomon et al., 2007; Ross et al., 2010; Koureas et al., 2012; Khan et al., 2019). In addition, farmers may be considering the sustainability of treatments. Dips are of environmental concern if not disposed of correctly (Scottish Environment Protection Agency, 2006) and are thought to be excreted in the urine and faeces of treated animals (Roberts & Hutson, 1999) and during wool production (Savage, 1998; Environment Agency, 1999). On the other hand, since resistance to the main MLs used to treat and prevent scab has been reported ((Doherty et al., 2018; Sturgess-Osborne et al., 2019), injection of MLS may also not be considered a sustainable option. Clearly, the treatment decisions taken by farmers are influenced

by many factors which will vary from farmer to farmer, while only economic costs were captured in this model. However, since the majority of farms are businesses, it can be assumed that economic concerns generally play an important role in farming decisions across most farms.

The model presented here considers a Farmer and their Neighbour, each with a flock of 500 ewes. The costs of prophylactic and therapeutic treatment will vary according to flock size (with economies of scale), and therefore the point at which prophylactic treatment becomes economically viable may vary with flock size and predicted ewe output in addition to the factors explored in the sensitivity analyses. A further limitation of this model is that it can only simulate a scenario with a single neighbour when in reality, farmers often have multiple neighbours. An extension of the model might consider the impact of group cooperation and how this dynamic would change the optimum strategy for the farmer; nevertheless, the current single-neighbour scenario is a useful first step in this approach.

6.6 CONCLUSIONS

The model outputs have shown that, given current scab prevalence and sheep scab treatment costs, prophylaxis employing OPs may only be economically viable in upland farms (long-acting ML injections may also be cost effective in upland regions where prevalence is above average, such as Wales). Using prophylaxis in lowland farms is not cost effective. However, identifying higher prevalence regional hotspots that could be good targets for economically viable prophylaxis programs may be a productive approach. Only subsidising the overall cost of prevention would incentivise lowland farmers to use prophylaxis, assuming treatment choices are economically rational. The costs associated with sheep scab control and treatment have been estimated for both upland and lowland farms and together with this model provide a useful insight into the underlying drivers informing management decisions by farmers and could be used with the results from the previous chapters in this thesis to help in policy formulation.

Chapter 7

GENERAL DISCUSSION

Sheep scab has impacts on both the health and the productivity of sheep, therefore, successful control is important on the grounds of both improved welfare and sustainable farm economics. In the last 10 years, a number of control schemes have been implemented, largely aimed at improving industry awareness, such as the national ADAS "Stamp Out Scab" campaign (Phillips, 2014). However, there is no evidence that any have succeeded in even reducing the prevalence of scab. In light of the recently confirmed resistance in *P. ovis* mites to three primary injectable macrocyclic lactones (MLs) used to treat and prevent scab (moxidectin, doramectin and ivermectin) (Doherty et al., 2018; Sturgess-Osborne et al., 2019), it is thought that the prevalence of sheep scab is likely to increase in future, increasing the urgency of coherent action before the problem becomes unmanageable. However, determining the nature of this action is difficult. Firstly, there is the question of who should take the action; government or industry? Should the measures implemented be the same in each region of Great Britain? What are the financial implications of potential control methods? Which treatments should be used? The results from this thesis provide some new understanding of some of the key issues and the models described here, following some further modification, will allow potential sheep scab treatment strategies to be analysed and offer the potential for rational, evidence-based guidance to optimal cost-effective scab management.

7.1 WHAT WOULD FUTURE CONTROL STRATEGIES FOR SCAB ENTAIL?

7.1.1 Who should lead future control strategies?

When planning future interventions for scab, it first must be decided who should take a lead on deciding and implementing the interventions. Looking at the history of scab in Great Britain, it seems that the government would be the best placed to do this. Government control and compulsory implementation led to the eradication of scab in 1952 (Watson, 1976). When scab was reintroduced in 1973, government control, although unsuccessful in achieving complete eradication, clearly had an important impact in combating scab in the following years; demonstrated by the increase in scab incidence seen immediately after these measures were lifted in 1992 (Bisdorff et al., 2006). Although there have been industry-led initiatives that have been carried out since 1992 (Animal Health and Welfare Wales, 2018), there is little evidence to show that these have led to a decrease in incidence, which is thought to have remained fairly constant over the past thirteen years (for example, scab prevalence in Wales was 17% in 2006 (Bisdorff et al., 2006), 20.5% in 2011 (Rose et al., 2009) and 15.8% in 2018 (Chivers et al., 2018). Therefore, it seems that as government-led control measures have had the most success in the past, they may be the most effective in the future, if political appetite for national disease management can be re-established.

Analysis of the elements of the centralised government-led control efforts that were successful may give insight into what is likely to be required in any successful control program. First government-led initiatives were compulsory, backed by legislation and were enforced. This resulted in better compliance and synchronisation of scab prophylaxis measures. Synchronisation of prophylaxis helps to avoid confusion over which products should be used and when; something which has been identified as an issue for farmers since deregulation in 1992 (Bisdorff & Wall, 2008). In addition, without synchronisation of treatments, when farmers have used prophylaxis, their flocks are still vulnerable to reinfection from neighbours who have not (Animal Health and Welfare Wales, 2018). However, at present, as shown here (Chapter 6), in most scenarios, farmers have no economic motivation to use prophylaxis for scab in Great Britain, apart from in areas where the risk is high and when the cost of

treatment is low. Here, the game theory model, where two neighbouring farmers were given the choice to use or not use prophylaxis for scab, only when using an OP dip in uplands was the Nash equilibrium to use prophylaxis, regardless of the neighbour's strategy. When using MLs in the uplands, the Nash equilibrium is to not use prophylaxis, even if synchronisation of treatment between the two farmers would lead to a more economical outcome for both of them, as they have no guarantee that the other farmer would also use prophylaxis. Furthermore, in the lowlands, even if they were to synchronise their treatments it would be more expensive for both farmers, since the risk of scab is low.

Given the importance of treatment synchronisation, enforcement should be reconsidered, but this would require a considerable investment in national veterinary surveillance and inspection infrastructure, which no longer exists to the same extent as it did during the first half of the 20th century (Woods, 2011). The use of penalties or subsidies could also be considered motivate farmers to comply (French et al., 1999). Only Government (local or national) has the ability to enforce compliance, through legislation, leading to the synchronisation of prophylaxis between farmers across the large areas. Even then, without inspection, there will be some farmers that do not comply and there may not be enough resources to monitor this. Nevertheless, government-led strategies are still the most likely to lead to the highest uptake of prophylaxis and it is hoped that the synchronisation of prophylaxis between farms would lead to more impactful outcomes. In addition, Government are the only stakeholder with the ability to enforce biosecurity measures when new outbreaks of scab occur. The lack of the ability to do this puts industry in a very weak position if it attempts to lead on the control of scab.

7.1.2 Potential control methods when reacting to new scab outbreaks

In Great Britain, when scab is detected in at least one sheep, the Sheep Scab Order requires therapeutic treatment to be applied to the whole flock and that the movement of infested sheep is restricted (MAFF, 1997). Local authorities are tasked to implement measures to control scab outbreaks if farmers do not comply (although in most cases they do not have the resources to either inspect flocks or manage

treatment). Furthermore, when scab cases are detected on common land, local authorities are required to notify of the need to clear sheep from these areas (MAFF, 1997). The current regulations are less rigorous than those imposed by the Sheep Scab Order of 1928 (until 1992). Under the former regulations, when scab was confirmed to be present in a flock, it was compulsory to treat or euthanise all members of not just the index but also the neighbouring flocks and to notify the authorities (Spence, 1951; ADAS, 2008). Re-enforcing the treatment of neighbouring flocks might help greatly in preventing reinfection of index farms.

Notification is currently only compulsory in Scotland (Scottish Government , 2010). Current survey data in the rest of Great Britain therefore is relatively unreliable, relying on farmers and veterinary surgeons to submit cases to APHA (Animal and Plant Health Agency), resulting in 'clusters' associated with the willingness and enthusiasm of individuals to do this. Hence the data do not give a good overall picture of scab prevalence, since the disease status of non-submissions is unknown (APHA, 2019b). Comprehensive notification data could be used to identify where control measures should be focused, monitor the impact of different control measures and to fit models for scab. Therefore, expanding the compulsory reporting of scab to the rest of Great Britain would be advantageous in optimising future control methods for reacting and preventing scab outbreaks.

7.1.3 Potential control methods for the prevention of scab

Although synchronisation of the application of prophylaxis for scab is thought to be advantageous (Animal Health and Welfare Wales, 2018), this does not necessarily mean that all farms need to participate. Various studies have identified hotspots (areas of above average infection) of scab in Great Britain and they suggest that these hotspots could be useful targets for future control programs where prophylaxis is used cooperatively between all farmers within the hotspot (O'Brien, 1999; Bisdorff et al., 2006; Rose et al., 2009; Phythian et al., 2013; Chivers et al., 2018). Not requiring prophylactic treatment to be used by every farm is not only important in light of resistance to MLs, but it would also reduce the environmental impact of treatment. It is also more cost-effective at a national scale, so long as it is not at the expense of

having the desired impact. However, synchronisation of treatments across all hotspots is still important, highlighting that coordination at a national level may be necessary, since hotspots do not necessarily fall within the neat local authority boundaries.

Some previous studies have identified hotspots quite broadly, stating that these are usually areas of common grazing (O'Brien, 1999; Bisdorff et al., 2006). Others have only provided hotspot data for some regions of Great Britain (Phythian et al., 2013; Chivers et al., 2018). One study used species distribution modelling to predict where scab might be located, based on survey scab prevalence data, (as well as elevation, sheep density, and climate (Rose et al., 2009). Although all of these findings are useful in identifying hotspots, they based on survey data which only gives a snapshot of the prevalence of scab at any one point. However, in Chapter 3 (Fig. 3.13) of this thesis, the network of neighbouring farms in Great Britain developed for the model, identified specific areas where infected farms are unlikely to pass scab to other farms via neighbour-to-neighbour contact ($R_0 < 1$), areas where farms are likely to cause an outbreak ($1<R_0<5$) and areas where >99% of all connected farms are likely to become infected ($R_0 < 5$). This provides information at a more detailed scale than Rose et al. (2009) or Chivers et. al (2018), and for the whole of Great Britain, rather than just for one country. However, the estimates for R_0 are unlikely to be completely accurate, since the network was built on the assumption that neighbouring farms are within a 2km radius of each other and the location of common grazing farms and the mixing rates between different types of farms were estimated using data from the literature. Current prevalence data would still be helpful in refining the hotspots, as the areas where $R_0 >1$ are only important if scab is introduced into these areas. Therefore, the between-farm transmission models presented here (Chapters 3 & 5) could be used if notification of scab cases was made compulsory across Great Britain, to predict where the current hotspots of scab could be.

Of particular interest from the results presented in Chapter 3 was the suggestion that scab would not spread nationally by farm-to farm contact alone, because of the uneven spatial distribution of farms. The results from the model simulations in Chapter 3 suggest and the results from Chapter 5 confirm that long-distance movements are important to the patterns seen, for example after reintroduction in

1972 (French et al., 1999), and therefore to achieve a national reduction in scab incidence, transmission through this route must be restricted. This is best achieved through better hygiene during transport and inspections at markets. Again, governments are the best placed to enforce such restrictions, which might be best applied at a time when fewer movements occur to minimise disruption to the proper working of the sheep industry. Again, more reliable data on transport and inspection would help to refine this strategy. Synchronised treatments within the areas of Great Britain where $R_0 > 1$, or which are predicted to be infected by the between-farm transmission model, could then be enforced, however, the impact and costs of this proposed intervention needs to be fully understood. The next step would be to use the Chapter 5 model to investigate the impact of synchronised treatment in hotspots versus a national synchronised treatment program.

Research is also required into the frequency with which synchronised prophylaxis in hotspots needs to be applied. In the first half of the 20th century, when treatment was enforced across the whole country, dipping twice a year (1984-1988) led to more marked declines in the number of reported cases, compared to when a single national summer dip was used in 1983 (French et al., 1999) and a marked decline in cases for some parts of the year compared to when a single autumn dip was used (Fig. 5.1). Therefore, it would be useful to run simulations of the model described in Chapter 5, with different frequencies of prophylaxis in hotspots in a one-year period. This might identify how many times per year would make this control method most effective.

To identify whether specific control methods are likely to be cost-effective, the model presented in Chapter 6 could be expanded to a spatial game theory model. Previous work has shown that spatial game theory models often give novel results, for example unconditional co-operators are often more successful in spatial prisoner dilemma games than in non-spatial (Lindgren & Nordahl, 1994). Clusters of co-operators have also been found to be successful even if there are defectors along the cluster boundaries (Hauert & Doebeli, 2004). The spatial game theory model could be built for farm clusters within hotspots, to see whether it is cost effective for farmers to treat in these areas. It could also be developed across the whole of Great Britain to look at this question at a wider scale.

7.1.4 What treatments should be used?

Most control strategies for scab and all of those discussed so far involve the use of chemical formulations to treat and prevent scab. Any future control strategy will need to determine which chemicals to use. It is thought that the organochloride acaricide, γ HCH (lindane), that was used in the national control programmes from 1948 onwards, played a central role in the eradication of scab in Great Britain (Kirkwood, 1985b). Lindane has not been licenced for use in Great Britain since 1984, due to concerns about environmental and operator safety and potential residues in exported lamb (Henderson, 1991) and so it is unlikely that it could be reintroduced again. It is unclear whether it is the chemical itself or the surrounding control measures that led to the success of Lindane, as it shares a similar residual activity to the organophosphates (OPs) that are used for immersion dipping today (Kirkwood & Quick, 1981; O'Brien, 1999). More research into novel acaricides is required. MLs are more popular with farmers than OP dips (Chivers et al., 2018). However, with resistance to injectable MLs now reported, their use may be relatively limited in the future. One concern is that both MLs and OP dips are used as treatments for other parasitic diseases of sheep so the more widespread use for routine scab control will hasten resistance in other parasites of sheep such as gastro-intestinal nematodes. All these issues must be considered when deciding on the best treatments to use.

New technologies such as the ELISA test for scab diagnosis (Nunn et al., 2011), may provide a valuable novel approach to future control strategies. The time between experimental introduction of mites and clinical signs of infestation has been shown to vary from 12 to 51 days (Babcock & Black, 1933; Bates, 1997a). However, if the ELISA test is used, then detection may occur more quickly and more accurately (Nunn et al., 2011). The ELISA has recently been shown to be able to detect subclinical infection (Hamer et al., 2019) and could be useful in a number of ways, for example, to help target treatments to individuals within a flock who are infected, rather than treating the whole flock. In addition, it can confirm treatment failures and successes, which would demonstrate when eradication has been achieved within a flock. It could be used as a regulator in markets to ensure that produce was scab-free

before being sold. The impact of the ELISA test in reducing the number of cases of scab could be predicted in future versions of the models described in Chapters 2,3,4 and 5 of this thesis.

Novel technological advances could have a major impact in the fight against scab and, once available, should be incorporated in future interventions. These include new acaricidal treatments, which may be easier to develop in light of the recent draft genome assembly of *P. ovis* (Burgess et al., 2018), the development of an effective vaccine (Burgess et al., 2016) or the use of alternative treatments such as biocontrol (Jiang et al., 2019) and essential oils (Perrucci et al., 1997; Wall & Bates, 2011; Shang et al., 2019). The current status of these technologies was discussed in Chapter 1. Arguably the most important of these technologies is the vaccine, which may have an important impact in reducing scab prevalence, if sufficiently protective. If vaccination was able to provide long term immunity, then its use would be a preferable method of prophylaxis compared to the current chemical treatments. Even if immunity provided was not long-term, it would likely have less impact on the environment. In addition, not all sheep would need to be treated. Modelling could be used to identify the threshold of the proportion of the population that must be vaccinated in order to prevent further spread of scab (the principle of herd immunity, (Metcalf et al., 2015)). However, considering the current vaccine for sheep scab (under development) only achieves a reduction of mite numbers of up to 56% and lesion size of less than 63% (Burgess et al., 2016), it appears unlikely that the vaccine will be routinely used for scab in the near future.

7.1.5 Future implementation?

Although it seems that government-led control measures for scab would be the most effective, government have limited resources and the general trend has been for animal-health services in the UK to become more decentralised and privatised (Geering et al., 2002). Government appear to believe that their role is in animal health surveillance is to co-ordinate other stakeholders (veterinarians, animal owners, diagnostic facilities, data analysts and other specialists) to guarantee that surveillance fulfils national needs. Their priorities are increasingly focused on public and societal needs, which do not always overlap with the priorities of industry (UK Surveillance

Forum, 2018). The APHA (Animal and Plant Health Agency) prioritise the control of diseases based on their impact and risk (Gibbens et al., 2016). Therefore, whether government would be willing to implement national control measures for scab will depend on the estimated risks of scab if the measures are not taken and the resulting benefit to the public and society in Great Britain. Hence greater centralised investment and control would appear unlikely.

Another aspect to consider when looking at the government's willingness to implement the control measures discussed here is the impact of the planned European Union (EU) exit by the United Kingdom. When this occurs, the UK government may choose to increase subsidies to sheep farming in order to compensate for the loss of EU subsidies and to support the industry until new trade agreements for animal products can be arranged (Department for Environment, Food and Rural Affairs- DEFRA, 2018b). This may change the amount of funds available to put towards tackling endemic animal diseases such as scab, although, DEFRA say that they aim to "maintain appropriate preparedness and capability to deal with animal and plant diseases" (APHA, 2019a).

One critical problem in suggesting greater national-level control is that responsibility for animal health has been devolved to the member countries of the UK and to the local authorities (Anon, 2016). Coordination between local authorities in England is mainly implemented through regional networks and groups and the National Animal Health and Welfare Panel (NAHWP) (APHA, 2018b). The UK nations, while still setting their own priorities for animal health, work together where priorities overlap to ensure that resources are used efficiently (UK Surveillance Forum, 2018). Although local and country administrations are more likely to be aware of resident issues and therefore make more informed decisions about how best to allocate resources in their region (APHA, 2018b) and although coordination measures are in place between them, devolution may make it more difficult to coordinate national programs than if control was at a national level (Anon, 2016). This can be avoided if the process is efficiently managed and progressive (Geering et al., 2002). However, even with successful coordination and cooperation between governmental bodies, control strategies for scab are unlikely to be successful without industry, retailers and consumers also complying (Spence, 1951).

7.2 ALTERNATIVES TO GOVERNMENT-LED CONTROL

If the government are unwilling or unable to implement the control strategies, the results from this thesis and the models produced could still be useful in industry initiatives. They could be used to advise farmers, for example, to encourage synchronisation of prophylaxis using OP dips in the uplands where this is cost-effective (Chapter 6). In addition, community prophylaxis cooperatives within the individual hotspots identified in Chapter 3 could be encouraged to form. Impactful visual aids for use by industry to demonstrate predictions of the outcomes of different treatment scenarios can be presented, either in the STEM graphical user interface (GUI) (Doerr et al., 2019) for the Chapter 2 and 3 models, or in a R shiny app (Chang et al., 2017) with animations for the models presented in Chapters 4 and 5.

7.3 WHAT ROLE DOES MODELLING HAVE IN DEVELOPING CONTROL STRATEGIES FOR DISEASE?

Epidemiological modelling is an established field of research which has produced results that increase understanding about past cases of diseases (Dean et al., 2019), has been used in real-time to anticipate the spread of current epidemics (Polonsky, 2019) and to guide surveillance before a pathogen has even been introduced into a population (Gottwald et al., 2019). Economic modelling of disease is also widely used to inform treatment decisions based on cost-effectiveness (Briggs et al., 2006). However, caution must be taken when assessing the results of models, as the models themselves are based on assumptions and can never reflect reality perfectly (Reeves et al., 2011). When possible, it is recommended that all relevant processes of the natural system are included initially in the model and then less-influential processes, identified by uncertainty and sensitivity analyses, are removed later (Murdoch et al., 1992). However, first, modellers must decide which system dynamics are considered to be relevant to include (Evans et al., 2013) and this can sometimes be subjective. Some modellers may believe that certain aspects are more important than others or may choose to represent these aspects in a different way to other modellers (Reeves

et al., 2011). Being aware of the aspects considered to be important by the modeller is important when assessing the results of a model.

It is also important to be aware of the limitations in the data used in the model, since the credibility of a model is influenced by the quality of data available (Rykiel, 1996). Models should be verified, to ensure their implementation in software matches that of the conceptual model (Reeves et al., 2011) and validated, to ensure they acceptably represent the system being modelled (Law & McComas, 2001). If these precautions are taken, then models can be a valuable guide when making decisions about disease control.

7.4 CONCLUSIONS

A number of control methods for sheep scab have been developed over the years, some more successful than others. When planning future interventions, the results presented in this thesis give suggestions towards the nature of these interventions if they are to be successful and economic. Looking at past control strategies and the fact that most farmers currently have no economic motivation to use preventative treatment for scab (Chapter 6), it seems that government-led national control for reactive and preventative treatment for sheep scab would have the most impact, although politically unlikely. For reactive treatment, it is thought that compulsory notification of scab cases should be introduced across the whole of Great Britain, rather than just for Scotland. It also could be useful to ensure neighbouring flocks of index farms are treated. In terms of prophylaxis for scab, it is suggested that introducing programmes of synchronised prophylaxis in hotspots might be the most practically effective, achievable and the most economic strategy. Compulsory notification of scab outbreaks would provide valuable data helping to predict the presence of hotspots more accurately. Results suggest that long-distance movements are particularly important for the spread of sheep scab so intervention at transport and markets is likely to be very important. Finally, the greater incorporation of new technologies such as the ELISA test might help to improve future control strategies, as well as other novel treatment methods; in particular, an effective vaccine could make a huge difference. Caution must be taken when using models such as those described in this thesis, as they are based upon assumptions and are limited by the

quality of data available. So long as these precautions are taken, then the models described in this thesis are constructive guides in the development of future control strategies for scab in Great Britain, with the primary aim of reducing the impact of this disease on the welfare and productivity of sheep.

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APPENDIX II

CHAPTER 2

Implementation of the disease model in STEM

It is possible to build a customised disease model in STEM using the model creator (Douglas, et al., 2013) based on an existing model in STEM. This generates source code from a model structure defined by the user in a graphical user interface. The first step is to configure a model package; here a package called com.sidp.diseasemodels.scab.sidp has been created. The built-in SI Compartment Model was expanded to incorporate the model feature described in Chapter 2. Additional parameters have been added to the SI model as described in Chapter 2 and shown as part of the transitions given in Table S.1. Within the Visual Model Editor, additional compartments were added, and transitions drawn between them as described by Douglas et al. (2013) and shown in Fig. S1. Within the expression editor, the appropriate expressions were written in STEM Expression Language (Betek et al., 2017) to describe the nature of each transition.

Workarounds in STEM

There are certain built-in features of STEM which are difficult to change, therefore, there were a number of workarounds needed in order to implement the model as was required.

Firstly, the built-in STEM deaths compartment does not allow any transitions to be added or taken from it. Since deaths are restocked as new susceptible sheep, a transition from D to S is needed and so a new compartment called D has been created and used in place of the built-in death compartment. There is a built-in infectious mortality rate in STEM associated with the built-in death compartment, however, a new parameter was established here to ensure that this is only counted as specified in Chapter 2 and not within the built-in disease deaths compartment. The

built-in parameter "infectious mortality rate" in STEM has been set to 0 and a new parameter called realinfectiousmortality has been created, which has the rate specified here. This ensures that STEM doesn't count the disease deaths twice.
In order to run the model in a batch mode, a dummy parameter, "experimental iterations", is created. This is used to determine the number of iterations in the batch mode when using the random seed for the stochastic solver.

In STEM, the protection rate (ψ) cannot be used if different control measures are to be implemented on different farms (when multiple farms are used in future expansions of the model described here) and therefore an alternative method is used to implement the movement of individuals from the "susceptible" and "infected" states to the treated state. This involved using the vaccinations() function in place of ΨS and the isolations() function in place of ΨI when writing the expressions for compartment transitions in the model creator (Douglas et al., 2013). This allows for the numbers of individuals moving from the susceptible and infected compartments to the treated compartments at each farm to be specified. The two functions were not created in STEM for this purpose (they were created to specify the number of vaccinations and isolations) (Betek et al., 2017; Douglas et al., 2018a), but were used successfully as described here. A control graph in STEM must also be created in order to allow for the implementation of these functions (Douglas et al., 2018a). If running the model stochastically, you need to make the proportion of vaccinations and isolations higher than 1 for it to be 100% probability e.g., 100).

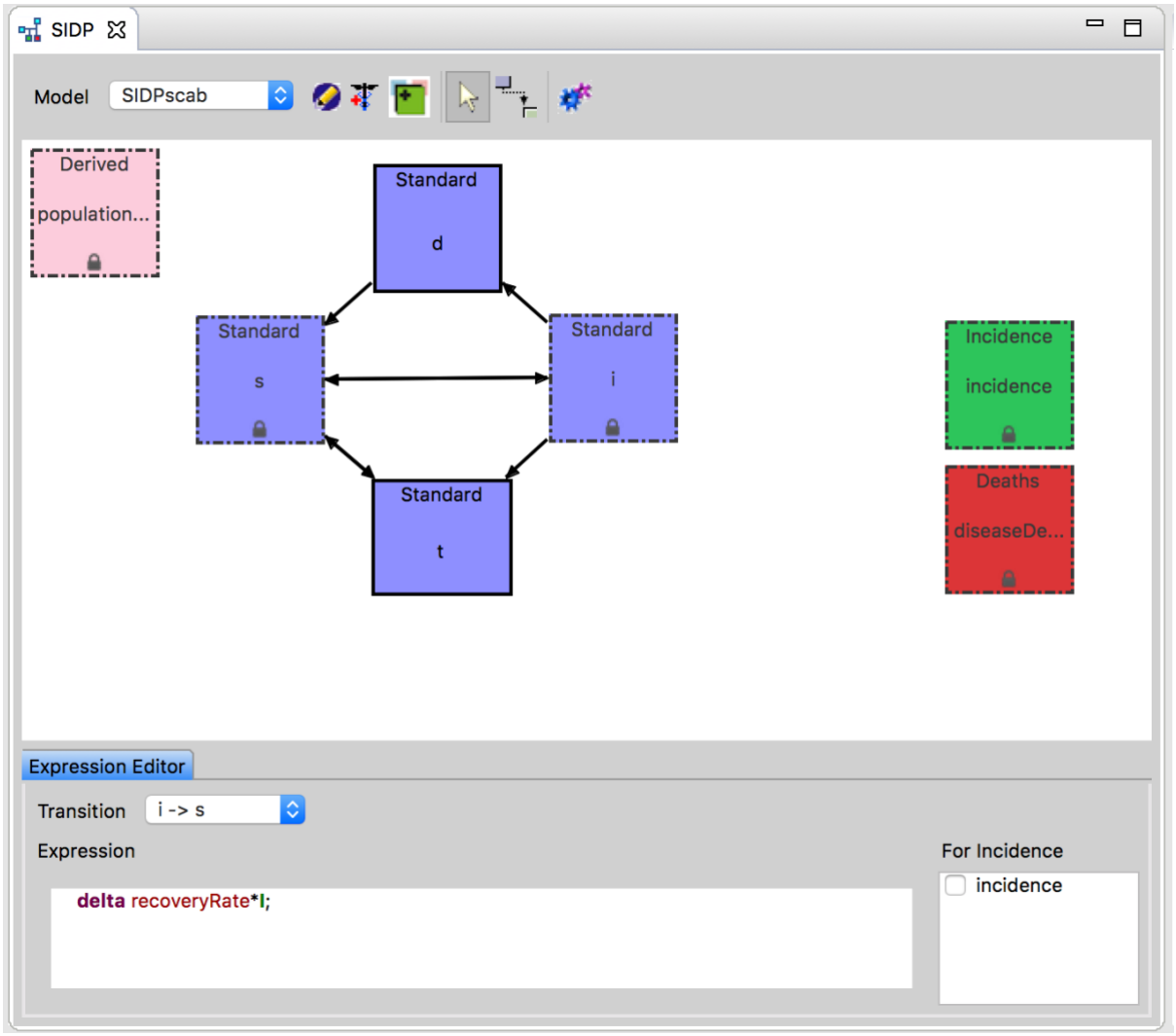

Fig. S.1 The transitions drawn between comparments in the Visual Editor in the STEM model creator for the STEM model described in Chapter 2.

Table S.1. The transition events and their associated transition rates for a SIDP model for sheep scab. Each transition involves the movement of individuals between classes. The number of individuals moving depends on the population size and parameter values. The classes are represented by the following variables: S = susceptible, I = infectious and P= treated. The coefficients are represented by: β= transmission rate, α= recovery rate, θ= protection rate and ψ= protection loss rate.

Event	**Transition**	**Rate**	**How this is written in STEM Expression Language**
Susceptible sheep becoming infected with scab	S -> I	βSI	delta transmissionRate*S*I; Have incidence selected
Infected sheep recovering and becoming susceptible to future infection	I -> S	αI	delta recoveryRate*I;
Susceptible sheep being treated prophylactically	S -> T	θS	delta isolations();
Infected sheep being treated reactively with a product that has residual activity	I -> T	θI	delta vaccinations();
Sheep that had been treated from getting scab (by treatment) now susceptible following the end of the treatment's residual activity	T -> S	ψS	delta protectionLossRate*T;
Infected sheep dying	I->D	γI	delta realinfectiousmortality*I;
Restocking to replace dead sheep	D->S	μ*D	Delta restockingRate*D;

Frequency and density dependency in STEM

In STEM, there is an option to select the model to be frequency or density dependent, which changes whether the area of a farm is used to scale the transmission rate or not (personal communication with Stefan Edlund and James Kaufman, the software authors). As we are assuming that the area is constant across all farms, the frequency dependent option is selected for the STEM models in Chapters 2 and 3. However, the model is still density-dependent in terms of the number of infected individuals and their density within a population due to how the transmission rate is scaled in the transmission term in the model equations.

In the STEM expressions (Table S1), an upper-case letter for a compartment is the actual number of individuals in that compartment and if the lower-case is used then this is divided by the total population size (N). Therefore, if you set your transmission term to βSi, then this is equivalent to the frequency-dependent transmission term $\beta' S \frac{I}{N}$ where the transmission term is scaled by the population size (N) and the number of contacts remains the same regardless of the population size. As the Chapter 2 and 3 models were density-dependent, βSI was used as the transmission term.

Miscellaneous parameters in STEM

Note that when parameters are entered into STEM, it isn't possible to enter fractions and so for all parameters, the decimal was given up to and including the recurring symbol.

Characteristic mixing distance

The characteristic mixing distance can be specified in STEM, but this is only for when mixing edges are used. In the Chapter 3 STEM model, bidirectional migration edges are used in place of mixing edges and so this parameter is unnecessary. The parameter is set to zero.

Nonlinearity coefficient (*y*)

This impacts the mass action term (βSI) as follows:

$$(SI)^y$$

In Chapter 2 and 3 STEM models, *y* is set to 1 as it is not necessary to modify the mass action term.

Reference population density

This is only used when you set the "frequency-dependent" parameter to false in STEM. The transmission rate is then scaled by the population density in every location by scaling factor populationDensity / referencePopulationDensity. Therefore, as "true" for the frequency-dependent parameter was selected from the Chapter 2 and 3 STEM models, then the value of the reference population density shouldn't have an impact. However, it will be set at 1, to ensure consistency.

Road network adjacent infectious proportion

The road network adjacent infectious proportion is left at 0 as a road network is not used in either of the STEM models.

Triggers, modifiers and predicates

Triggers with modifiers and predicates are used in STEM (Douglas, et al., 2018) to change the values of these two parameters at different stages of the simulation and for specified lengths of time. This allows for the residual activity of the two main treatments in use for sheep scab to be modelled.

Implementing stochasticity in STEM

STEM has built in "solvers" which are able to integrate the differential equations in models (Kaufman, et al., 2019a). This includes a number of deterministic solvers, as well as the stochastic solver, which is what was used in the STEM models in Chapters 2 and 3.

With the stochastic solver, an ordinary differential equations solver is still used to integrate within a time step and the noise is added at the end of each simulation time step. Each transition is drawn from a discrete binomial distribution, resulting in integer counts of individuals moving between states.

Stochastic seeds

The experiment mode in STEM can be used to run the model in batch mode using different stochastic seeds.

(1) Set the "Randomise seed" parameter in the stochastic solver to true

(2) Create a modifier for the disease. A parameter called "Experimental_iterations" has been created in my model produced in the model

generator. Select a range of integers to iterate over (to determine how many times to run the model with a different seed)

(3) Add the scenario you want to run and the modifier to a new experiment

The number of different seeds to use should be determined by the point at which the results reach stability i.e., the result is not affected by the addition of more seeds. Note, within a flock this might never happen (especially if you are starting with a different number of infecteds each run of the model), however, this should happen when looking at farm-farm transmission.

R function for the Chapter 2 deterministic SIDT model

```
SIDT.dyn <- function(t,var,par) {

 S <- var[1]
 I <- var[2]
 D <- var[3]
 P <- var[4] #This is the equivalent to compartment T in the chapter
 N <- S + I + D + P

 beta <- par[1]
 gamma <- par[2]
 san <- par[3]
 xi <- par[4]
 psi <- par[5]
 theta <- par[6]

 dS <- (gamma*I) + (xi*D) + (theta*P) - (beta * S * I) - (psi * S)
 dI <- (beta * S * I) - (gamma*I) - (san*I) - (psi*I)
 dD <- (san*I) - (xi*D)
 dP <- psi*(I+S) - (theta * P)

 list(c(dS, dI, dD, dP))


}
```

Table S2. The number of cases in each county by year in the MAFF data and in a randomly selected stochastic run of the Chapter 3 model for the years given in Fig. 3.20-3.29.

Year	County	Number of cases in simulations	Number of cases in MAFF data
1973	CHESHIRE	443	1
1973	CLWYD	36	0
1973	CUMBRIA	59	0
1973	DERBYSHIRE	1021	6
1973	DEVON	0	1
1973	DURHAM	669	0
1973	GREATERMANCHESTER	168	0
1973	LANCASHIRE	1842	17
1973	MONTGOMERYSHIRE	0	3
1973	NORTHYORKSHIRE	2017	0
1973	NOTTINGHAMSHIRE	5	0
1973	SHROPSHIRE	287	3
1973	STAFFORDSHIRE	978	1
1973	WESTMIDLANDS	4	0
1973	YORKSHIRE	3336	35
1974	BORDERS	0	1
1974	CHESHIRE	465	0
1974	CLWYD	4941	3
1974	CUMBRIA	65	0
1974	DERBYSHIRE	1021	0
1974	DEVON	0	2
1974	DURHAM	786	0
1974	DYFED	1	0
1974	GLOUCESTERSHIRE	541	0
1974	GREATERMANCHESTER	174	0
1974	GWENT	833	0
1974	GWYNEDD	163	0
1974	HEREFORDSHIRE	1434	0
1974	LANCASHIRE	1844	0
1974	MIDGLAMORGAN	117	0
1974	NORTHUMBERLAND	22	0

1974	NORTHYORKSHIRE	2142	0
1974	NOTTINGHAMSHIRE	5	0
1974	POWYS	2990	0
1974	SHROPSHIRE	1710	5
1974	SOUTH GLAMORGAN	127	0
1974	STAFFORDSHIRE	985	0
1974	STRATHCLYDE	0	6
1974	SURREY	0	1
1974	TYNEANDWEAR	9	0
1974	WESTMIDLANDS	4	0
1974	WORCESTERSHIRE	376	0
1974	YORKSHIRE	3336	10
1975	AVON	0	3
1975	BEDFORDSHIRE	0	2
1975	BERKSHIRE	0	1
1975	BORDERS	0	1
1975	BUCKINGHAMSHIRE	2	15
1975	CAMBRIDGESHIRE	0	2
1975	CHESHIRE	465	0
1975	CLWYD	1656	0
1975	CORNWALL	0	1
1975	CUMBRIA	73	0
1975	DERBYSHIRE	1021	5
1975	DEVON	0	14
1975	DORSET	0	3
1975	DUMFRIES GALLOWAY	0	1
1975	DURHAM	787	0
1975	DYFED	1	1
1975	GLOUCESTERSHIRE	2091	6
1975	GRAMPIAN	0	1
1975	GREATERMANCHESTER	175	0
1975	GWENT	833	0
1975	GWYNEDD	163	0
1975	HEREFORD WORCESTER	0	6
1975	HEREFORDSHIRE	1437	0
1975	HUMBERSIDE	0	1
1975	KENT	0	1
1975	LANCASHIRE	1844	0
1975	LEICESTERSHIRE	175	2
1975	LINCOLNSHIRE	0	3
1975	MIDGLAMORGAN	140	0

1975	NORTHAMPTONSHIRE	1209	21
1975	NORTHUMBERLAND	66	3
1975	NORTHYORKSHIRE	2106	0
1975	NOTTINGHAMSHIRE	5	0
1975	OXFORDSHIRE	294	24
1975	POWYS	3013	0
1975	SHROPSHIRE	1711	3
1975	SOMERSET	0	4
1975	SOUTH GLAMORGAN	129	1
1975	STAFFORDSHIRE	985	4
1975	TYNEANDWEAR	9	0
1975	WARWICKSHIRE	487	3
1975	WEST MIDLANDS	0	1
1975	WESTMIDLANDS	58	0
1975	WILTSHIRE	0	2
1975	WORCESTERSHIRE	718	0
1975	YORKSHIRE	5004	42
1980	BUCKINGHAMSHIRE	2	1
1980	CHESHIRE	465	0
1980	CLWYD	1635	0
1980	CORNWALL	0	5
1980	CUMBRIA	42	0
1980	DERBYSHIRE	1021	0
1980	DEVON	0	7
1980	DORSET	0	1
1980	DURHAM	820	0
1980	DYFED	1	0
1980	GLOUCESTERSHIRE	2100	3
1980	GREATERMANCHESTER	175	0
1980	GWENT	833	0
1980	GWYNEDD	165	0
1980	HEREFORD WORCESTER	0	2
1980	HEREFORDSHIRE	1440	0
1980	KENT	0	2
1980	LANCASHIRE	1846	0
1980	LEICESTERSHIRE	175	1
1980	MIDGLAMORGAN	141	0
1980	NORTHAMPTONSHIRE	2821	15
1980	NORTHUMBERLAND	22	0
1980	NORTHYORKSHIRE	2096	0
1980	NOTTINGHAMSHIRE	5	0

1980	OXFORDSHIRE	294	6
1980	POWYS	3017	0
1980	SHROPSHIRE	1713	0
1980	SOUTH GLAMORGAN	129	0
1980	STAFFORDSHIRE	2955	4
1980	TYNEANDWEAR	9	0
1980	WARWICKSHIRE	487	3
1980	WEST SUSSEX	0	1
1980	WESTMIDLANDS	56	0
1980	WILTSHIRE	0	2
1980	WORCESTERSHIRE	721	0
1980	YORKSHIRE	1670	0
1984	BORDERS	0	2
1984	BUCKINGHAMSHIRE	2	0
1984	CHESHIRE	465	2
1984	CLEVELAND	0	1
1984	CLWYD	4884	3
1984	CORNWALL	0	11
1984	CUMBRIA	39	18
1984	DERBYSHIRE	1021	4
1984	DEVON	0	19
1984	DORSET	0	2
1984	DUMFRIES GALLOWAY	0	2
1984	DURHAM	2454	12
1984	DYFED	1	2
1984	EAST SUSSEX	0	3
1984	GLOUCESTERSHIRE	698	0
1984	GREATERMANCHESTER	175	0
1984	GWENT	833	1
1984	GWYNEDD	163	0
1984	HEREFORD WORCESTER	0	9
1984	HEREFORDSHIRE	1443	0
1984	KENT	0	5
1984	LANCASHIRE	1846	9
1984	LEICESTERSHIRE	175	3
1984	LINCOLNSHIRE	0	1
1984	LOTHIAN	0	3
1984	MIDGLAMORGAN	426	3
1984	NORTHAMPTONSHIRE	403	0
1984	NORTHUMBERLAND	22	0
1984	NORTHYORKSHIRE	2062	0

1984	NOTTINGHAMSHIRE	5	2
1984	OXFORDSHIRE	98	1
1984	POWYS	3012	3
1984	SHROPSHIRE	1712	11
1984	SOMERSET	0	11
1984	SOUTH GLAMORGAN	129	0
1984	STAFFORDSHIRE	985	3
1984	TYNEANDWEAR	9	0
1984	WARWICKSHIRE	487	1
1984	WESTMIDLANDS	56	0
1984	WORCESTERSHIRE	720	0
1984	YORKSHIRE	5010	48
1988	BUCKINGHAMSHIRE	2	0
1988	CHESHIRE	465	4
1988	CLWYD	4869	3
1988	CORNWALL	0	3
1988	CUMBRIA	26	0
1988	DERBYSHIRE	1021	2
1988	DEVON	0	2
1988	DORSET	0	3
1988	DURHAM	822	0
1988	DYFED	1	0
1988	GLOUCESTERSHIRE	694	1
1988	GREATERMANCHESTER	174	0
1988	GWENT	833	1
1988	GWYNEDD	163	3
1988	HEREFORD WORCESTER	0	1
1988	HEREFORDSHIRE	1443	0
1988	LANCASHIRE	1825	0
1988	LEICESTERSHIRE	175	0
1988	LINCOLNSHIRE	0	2
1988	LOTHIAN	0	1
1988	MIDGLAMORGAN	417	9
1988	NORTHAMPTONSHIRE	403	0
1988	NORTHUMBERLAND	22	0
1988	NORTHYORKSHIRE	2016	0
1988	NOTTINGHAMSHIRE	5	0
1988	OXFORDSHIRE	98	0
1988	POWYS	3004	1
1988	SHROPSHIRE	1710	3
1988	SOMERSET	0	4

1988	SOUTH GLAMORGAN	129	0
1988	STAFFORDSHIRE	985	0
1988	TYNEANDWEAR	9	0
1988	WARWICKSHIRE	487	1
1988	WESTMIDLANDS	56	0
1988	WORCESTERSHIRE	720	0
1988	YORKSHIRE	1670	0
1989	AVON	0	1
1989	BORDERS	0	1
1989	BUCKINGHAMSHIRE	2	0
1989	CAMBRIDGESHIRE	0	1
1989	CHESHIRE	465	0
1989	CLWYD	4866	6
1989	CORNWALL	0	17
1989	CUMBRIA	20	0
1989	DERBYSHIRE	1021	1
1989	DEVON	0	13
1989	DORSET	0	3
1989	DURHAM	822	0
1989	DYFED	1	1
1989	ESSEX	0	1
1989	GLOUCESTERSHIRE	694	0
1989	GREATERMANCHESTER	173	0
1989	GWENT	833	0
1989	GWYNEDD	163	1
1989	HEREFORD WORCESTER	0	3
1989	HEREFORDSHIRE	1441	0
1989	LANCASHIRE	1813	0
1989	LEICESTERSHIRE	175	0
1989	MERSEYSIDE	0	1
1989	MIDGLAMORGAN	139	0
1989	NORTHAMPTONSHIRE	403	0
1989	NORTHUMBERLAND	22	0
1989	NORTHYORKSHIRE	2008	0
1989	NOTTINGHAMSHIRE	5	0
1989	OXFORDSHIRE	98	0
1989	POWYS	3008	1
1989	SHROPSHIRE	1708	3
1989	SOMERSET	0	11
1989	SOUTH GLAMORGAN	129	0
1989	STAFFORDSHIRE	985	2

1989	TYNEANDWEAR	9	0
1989	WARWICKSHIRE	487	0
1989	WESTMIDLANDS	56	0
1989	WILTSHIRE	0	4
1989	WORCESTERSHIRE	720	0
1989	YORKSHIRE	1668	0
1990	AVON	0	2
1990	BEDFORDSHIRE	0	3
1990	BUCKINGHAMSHIRE	2	0
1990	CAMBRIDGESHIRE	0	1
1990	CHESHIRE	465	2
1990	CLWYD	4848	12
1990	CORNWALL	0	11
1990	CUMBRIA	10	0
1990	DERBYSHIRE	1021	7
1990	DEVON	0	6
1990	DORSET	0	1
1990	DURHAM	825	0
1990	DYFED	1	0
1990	GLOUCESTERSHIRE	693	4
1990	GRAMPIAN	0	2
1990	GREATERMANCHESTER	173	0
1990	GWENT	833	0
1990	GWYNEDD	163	3
1990	HEREFORD WORCESTER	0	2
1990	HEREFORDSHIRE	1440	0
1990	HERTFORDSHIRE	0	1
1990	HUMBERSIDE	0	5
1990	LANCASHIRE	1774	9
1990	LEICESTERSHIRE	175	2
1990	LINCOLNSHIRE	0	1
1990	MERSEYSIDE	0	1
1990	MIDGLAMORGAN	138	0
1990	NORFOLK	0	7
1990	NORTHAMPTONSHIRE	403	0
1990	NORTHAMTONSHIRE	0	6
1990	NORTHUMBERLAND	22	1
1990	NORTHYORKSHIRE	1982	0
1990	NOTTINGHAMSHIRE	5	1
1990	OXFORDSHIRE	98	1
1990	POWYS	3003	1

1990	SHROPSHIRE	1707	3
1990	SOMERSET	0	6
1990	SOUTH GLAMORGAN	129	0
1990	STAFFORDSHIRE	985	1
1990	STRATHCLYDE	0	1
1990	SUFFOLK	0	1
1990	TYNEANDWEAR	9	0
1990	WARWICKSHIRE	487	0
1990	WESTMIDLANDS	56	0
1990	WORCESTERSHIRE	719	0
1990	YORKSHIRE	1668	0
1991	AVON	0	1
1991	BEDFORDSHIRE	0	2
1991	BORDERS	0	2
1991	BUCKINGHAMSHIRE	2	1
1991	CHESHIRE	465	1
1991	CLWYD	1606	0
1991	CORNWALL	0	15
1991	CUMBRIA	7	0
1991	DERBYSHIRE	1021	3
1991	DEVON	0	15
1991	DORSET	0	2
1991	DURHAM	817	0
1991	DYFED	1	3
1991	EAST SUSSEX	0	3
1991	ESSEX	0	2
1991	GLOUCESTERSHIRE	691	12
1991	GREATER MANCHESTER	0	4
1991	GREATERMANCHESTER	172	0
1991	GWENT	833	4
1991	GWYNEDD	163	7
1991	HEREFORD WORCESTER	0	1
1991	HEREFORDSHIRE	1438	0
1991	LANCASHIRE	1762	12
1991	LEICESTERSHIRE	175	5
1991	LINCOLNSHIRE	0	1
1991	MIDGLAMORGAN	411	6
1991	NORFOLK	0	2
1991	NORTHAMPTONSHIRE	403	0
1991	NORTHAMTONSHIRE	0	1
1991	NORTHUMBERLAND	22	0

1991	NORTHYORKSHIRE	1927	0
1991	NOTTINGHAMSHIRE	5	0
1991	OXFORDSHIRE	98	1
1991	POWYS	2989	0
1991	SHROPSHIRE	1707	1
1991	SOMERSET	0	3
1991	SOUTH GLAMORGAN	129	0
1991	STAFFORDSHIRE	985	2
1991	SUFFOLK	0	2
1991	TAYSIDE	0	3
1991	TYNEANDWEAR	9	0
1991	WARWICKSHIRE	487	0
1991	WESTMIDLANDS	56	0
1991	WORCESTERSHIRE	715	0
1991	YORKSHIRE	3332	30
1992	AVON	0	2
1992	BUCKINGHAMSHIRE	2	1
1992	CENTRAL	0	5
1992	CHESHIRE	465	3
1992	CLWYD	4764	9
1992	CORNWALL	0	5
1992	CUMBRIA	0	1
1992	DERBYSHIRE	1021	1
1992	DEVON	0	14
1992	DORSET	0	1
1992	DUMFRIES GALLOWAY	0	1
1992	DURHAM	790	0
1992	DYFED	1	5
1992	GLOUCESTERSHIRE	680	0
1992	GRAMPIAN	0	5
1992	GREATER MANCHESTER	0	1
1992	GREATERMANCHESTER	169	0
1992	GWENT	833	0
1992	GWYNEDD	163	5
1992	HEREFORDSHIRE	1432	0
1992	LANCASHIRE	1686	6
1992	LEICESTERSHIRE	175	4
1992	LINCOLNSHIRE	0	3
1992	LOTHIAN	0	2
1992	MIDGLAMORGAN	136	0
1992	NORTHAMPTONSHIRE	403	0

1992	NORTHUMBERLAND	22	1
1992	NORTHYORKSHIRE	1916	0
1992	NOTTINGHAMSHIRE	5	2
1992	OXFORDSHIRE	98	0
1992	POWYS	2977	2
1992	SHROPSHIRE	1698	2
1992	SOMERSET	0	4
1992	SOUTH GLAMORGAN	129	0
1992	STAFFORDSHIRE	985	2
1992	STRATHCLYDE	0	3
1992	TAYSIDE	0	1
1992	TYNEANDWEAR	9	0
1992	WARWICKSHIRE	487	2
1992	WESTMIDLANDS	56	0
1992	WILTSHIRE	0	2
1992	WORCESTERSHIRE	705	0
1992	YORKSHIRE	4986	30

R function for the Chapter 4 deterministic SICTD model


```
library(deSolve)
SIDT.dyn <- function(t,var,par) {

  S <- var[1]
  I <- var[2]
  C <- var[3]
  D <- var[4]
  P <- var[5] #P is the equivalent to the T compartment in the Chapter

  N <- S + I + C  + P #haven't included D because I don't want it to be included in
births and deaths

 natbirthdeath <- par[1]
  beta <- par[2]
  epsilon <- par[3]
  gamma <- par[4]
  q <- par[5]
  tau <- par[6]
  restock <- par[7]
  stopprotect <- par[8]
  protect <- par[9]
  mortality <- par[10]

 dS <- natbirthdeath*N -(beta*I + epsilon*beta*C)*S + (gamma*(1-q)*I) + (tau*C)
+ (restock*D) + (stopprotect*P) - (protect*S)- natbirthdeath*S
  dI <-  (beta*I + epsilon*beta*C)*S - (gamma*I) - (mortality*I) - (protect*I) -
natbirthdeath*I
  dC <- (gamma*q*I) - (tau*C) - (protect*C)- natbirthdeath*C
  dD <- (mortality*I) - (restock*D) #no natural death rate from this because they
have already died
  dP <- protect*(I+C+S) - (stopprotect*P)- natbirthdeath*P

  list(c(dS, dI, dC, dD, dP))


}
```

R function for the stochastic SICTD model


```
library(GillespieSSA)

StochSICDP.dyn <- function(N, S0, I0, C0, D0, P0, natbirthdeath, beta, epsilon,
gamma, q, taw, restock, stopprotect, protect, mortality, f_time) {

  #replaced epsilon with e and tau with taw these are both parameters already in
GillespieSSA
  parms <- c(natbirthdeath = natbirthdeath, beta = beta, e = e, gamma = gamma, q
= q, taw = taw, restock = restock, stopprotect = stopprotect, protect = protect,
mortality = mortality)
  initial_state <- c(S= S0, I = I0, C = C0, D = D0, P = P0)
  final_time <- f_time

  rates <- c("natbirthdeath*N", "natbirthdeath*S", "natbirthdeath*I",
"natbirthdeath*C", "natbirthdeath*P", "(beta*I + e*beta*C)*S", "(gamma*(1-q)*I)",
"(gamma*q*I)", "(taw*C)", "(mortality*I)", "(restock*D)",
           "protect*S", "protect*I", "protect*C", "(stopprotect*P)")

  events <- matrix(c(1,0,0,0,0,
                     -1,0,0,0,0,
                     0,-1,0,0,0,
                     0,0,-1,0,0,
                     0,0,0,0,-1,
                     -1,1,0,0,0,
                     1,-1,0,0,0,
                     0,-1,1,0,0,
                     1,0,-1,0,0,
                     0,-1,0,1,0,
                     1,0,0,-1,0,
                     -1,0,0,0,1,
                     0,-1,0,0,1,
                     0,0,-1,0,1,
                     1,0,0,0,-1), 5,15)
  colnames(events) <- rates
  rownames(events) <- c("S", "I", "C", "D", "P")

  return(ssa(initial_state, rates, events, parms, final_time, method =
ssa.d()))#method= ssa.etl()))#,tau = 3))


}
```

Groups used in the Kruskal Wallis rank sum test for gamma

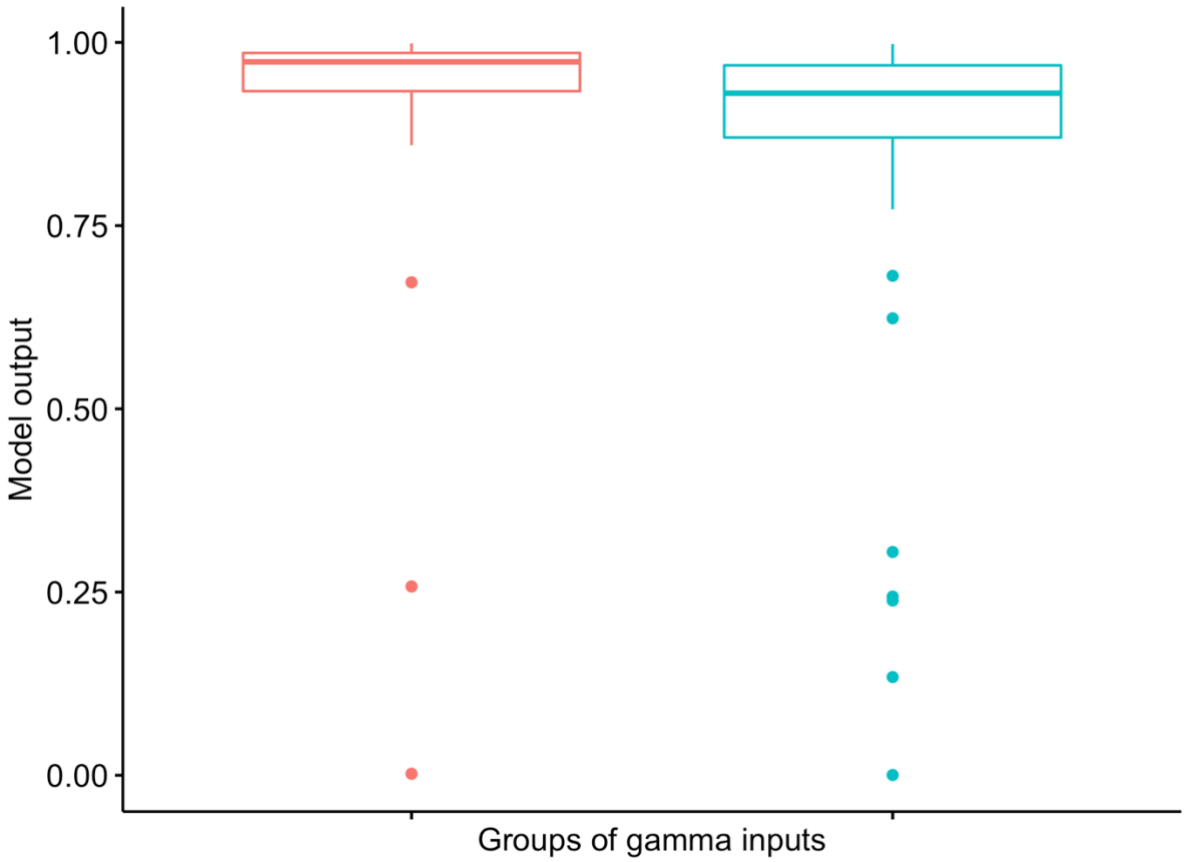

Fig. S.2 The range between the model output from 2 groups of 50 gamma inputs from Latin Hypercube Sampling of Parameter Set 1 used in the Kruskal Wallis rank sum test for gamma. The model output given is the fraction of the flock that are either infected or carriers on day 3650.

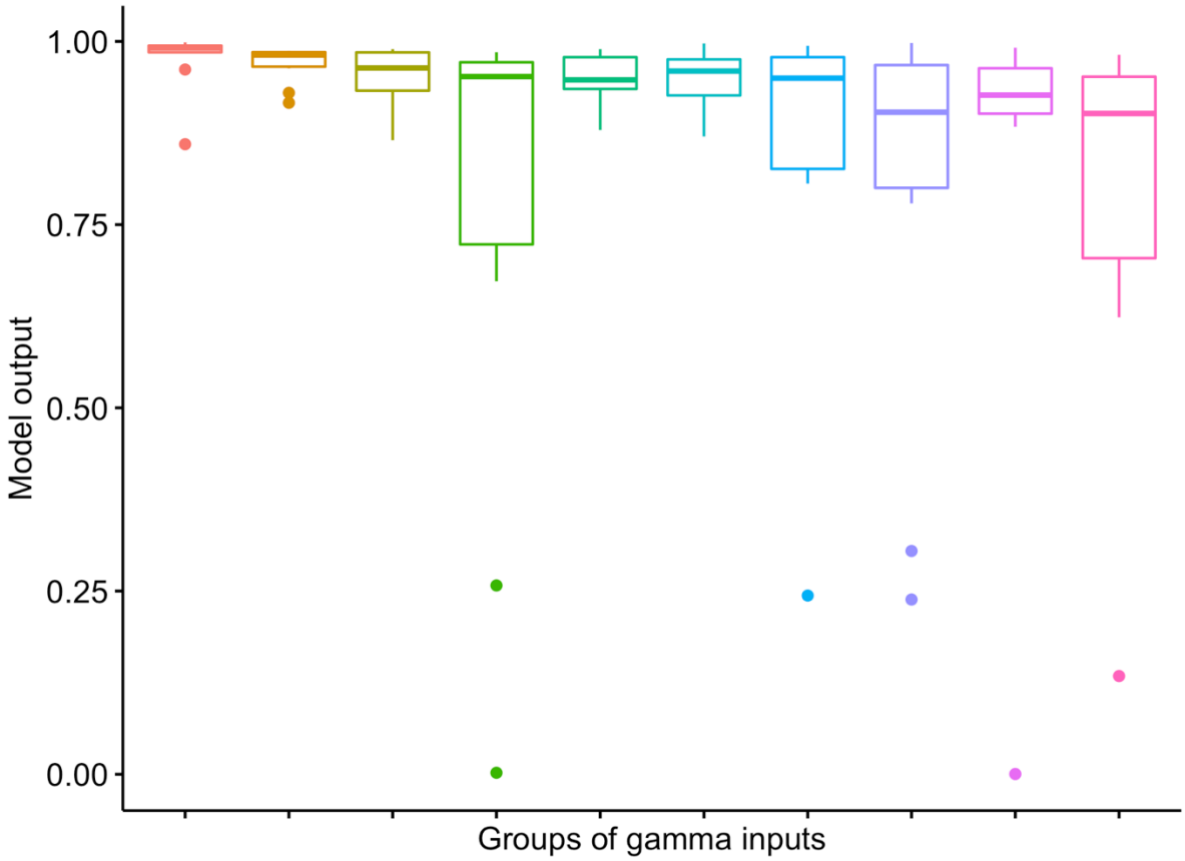

Fig. S.3 The range of model output between 10 groups of 10 gamma inputs from Latin Hypercube Sampling of Parameter Set 1 used in the Kruskal Wallis rank sum test for gamma. The model output given is the fraction of the flock that are either infected or carriers on day 3650.

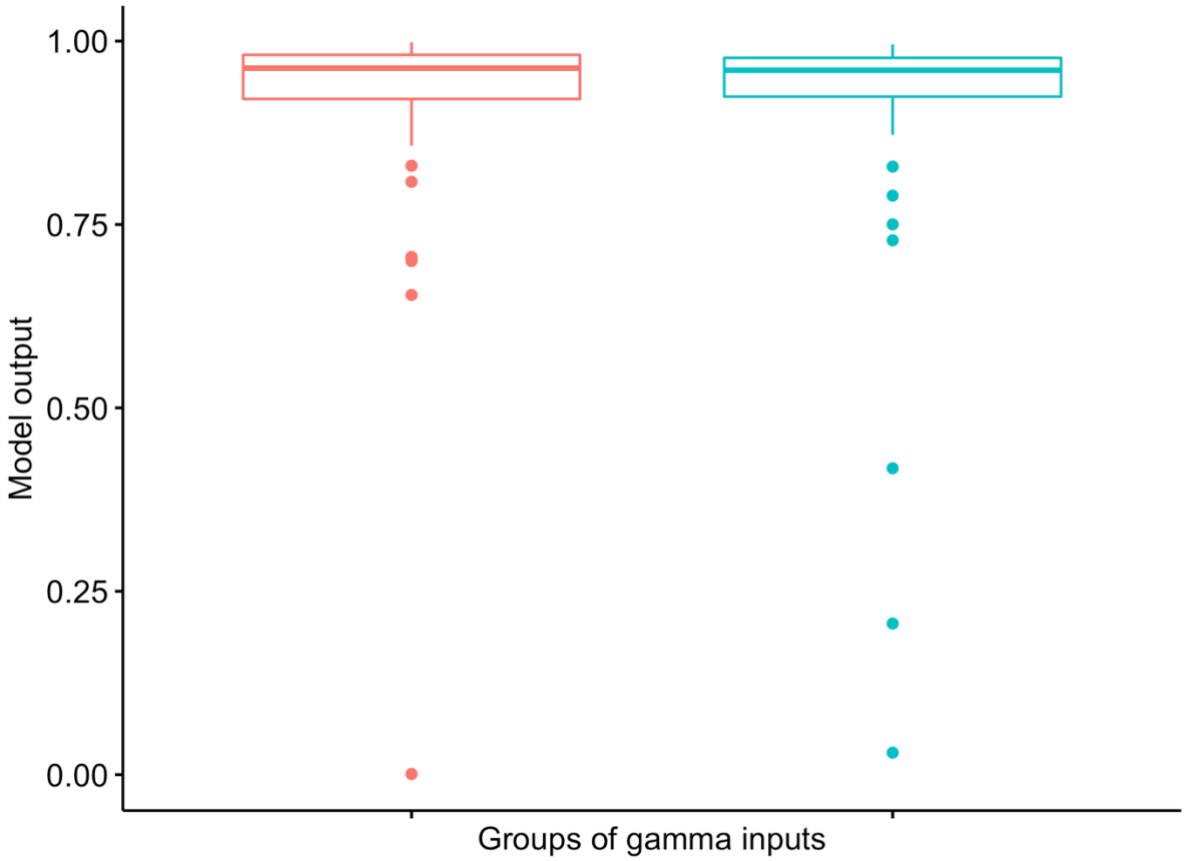

Fig. S.4 The range of model output from 2 groups of 50 gamma inputs from Latin Hypercube Sampling of Parameter Set 2 used in the Kruskal Wallis rank sum test for gamma. The model output given is the fraction of the flock that are either infected or carriers on day 3650.

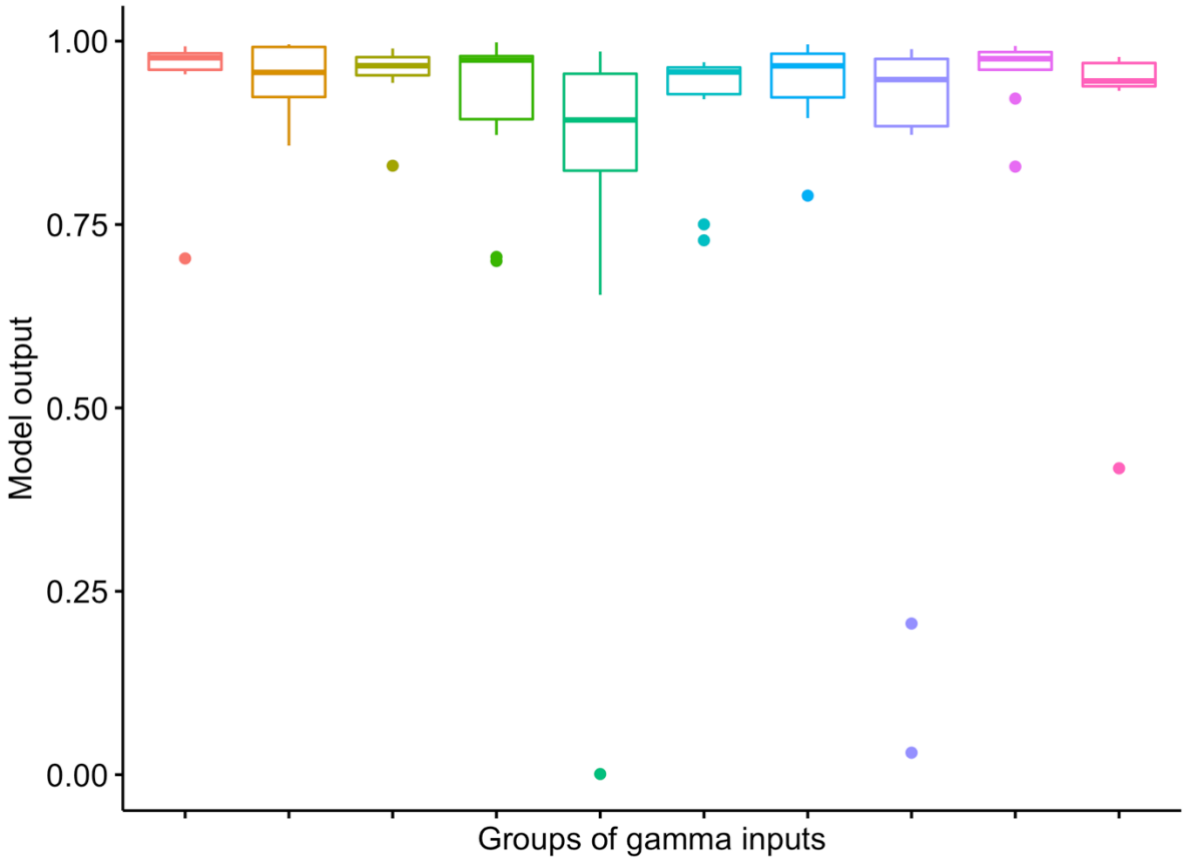

Fig. S.5 The range of model output between 10 groups of 10 gamma inputs from Latin Hypercube Sampling of Parameter Set 2 used in the Kruskal Wallis rank sum test for gamma. The model output given is the fraction of the flock that are either infected or carriers on day 3650.

The SimInf package (Widgren et al., 2019) was downloaded from GitHub on the 20th April 2020 and saved in a folder, the relevant C and R code adapted within this folder as outlined below and then the package installed locally by using the terminal to navigate to the folder and then using the "make install" command. The source code is under a GNU General Public License, with permissions for commercial use, modification, distribution, patent use and private use, but with no warranty or liability included. The conditions of the permissions is that a license and copyright notice is given, that the changes made are stated, that the source is disclosed and that the modified source code is also licensed with a GNU General Public License. The modified code presented here is also subject to the same GNU General Public License (which is included at the end of the Appendix) and, as with the whole thesis, additionally under a CC BY NC ND licence (in future it may be made available under a different license on GitHub- username emjnixon15). The changes I made to the source code here are highlighted in red.

The following is the adapted C code for the SISe_Sp model with comments and changes I have made highlighted in red:

```
/*
 * This file is part of SimInf, a framework for stochastic
 * disease spread simulations.
 *
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 * Copyright (C) 2017 -- 2019 Robin Eriksson
 * Copyright (C) 2015 -- 2019 Stefan Engblom
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 * (at your option) any later version.
 *
```

```
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the
 * GNU General Public License for more details.
 *
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 * along with this program.  If not, see <https://www.gnu.org/licenses/>.
 */

#include "SimInf.h"
#include "SimInf_forward_euler_linear_decay.h"
#include "SimInf_local_spread.h"

/* Offset in integer compartment state vector */
/* Added in my extra compartments here, H is the same as the T compartment in
the chapter */
enum {S, I, C, D, H};

/* Offset in real-valued continuous state vector */
enum {PHI};

/* Offsets in node local data (ldata) to parameters in the model */
enum {END_T1, END_T2, END_T3, END_T4, NEIGHBOR};

/* Offsets in global data (gdata) to parameters in the model */
/* I've added new parameters called epar, tau, qprop, dismortality and restock */
enum {UPSILON, GAMMA, ALPHA, BETA_T1, BETA_T2, BETA_T3,
BETA_T4, COUPLING, EPAR, TAU, QPROP, DISMORTALITY, RESTOCK};

/**
 * susceptible to infected: S -> I
 *
 * @param u The compartment state vector in node.
```

```
 * @param v The continuous state vector in node.
 * @param ldata The local data vector for the node.
 * @param gdata The global data vector.
 * @param t Current time.
 * @return propensity.
 */
double SISe_sp_S_to_I(
    const int *u,
    const double *v,
    const double *ldata,
    const double *gdata,
    double t)
{
    return gdata[UPSILON] * v[PHI] * u[S];
}

/**
 *  infected to susceptible: I -> S (EDITED)
 *
 * @param u The compartment state vector in node.
 * @param v The continuous state vector in node.
 * @param ldata The local data vector for node.
 * @param gdata The global data vector.
 * @param t Current time.
 * @return propensity.
 */
double SISe_sp_I_to_S(
    const int *u,
    const double *v,
    const double *ldata,
    const double *gdata,
    double t)
{
    return gdata[GAMMA] * (1- gdata[QPROP]) * u[I];
```

```
    /* Have changed the above so that it includes infecteds only going to the
susceptible - some need to become carriers */
}


/**
 *  infected to carriers: I -> C (NEW)
 *
 * @param u The compartment state vector in node.
 * @param v The continuous state vector in node.
 * @param ldata The local data vector for node.
 * @param gdata The global data vector.
 * @param t Current time.
 * @return propensity.
 */
double SISe_sp_I_to_C(
    const int *u,
    const double *v,
    const double *ldata,
    const double *gdata,
    double t)
{
  return gdata[GAMMA] * gdata[QPROP] * u[I];

}

/**
 *  infected to disease death: I -> D (NEW)
 *
 * @param u The compartment state vector in node.
 * @param v The continuous state vector in node.
 * @param ldata The local data vector for node.
 * @param gdata The global data vector.
 * @param t Current time.
```

```
 * @return propensity.
 */
double SISe_sp_I_to_D(
    const int *u,
    const double *v,
    const double *ldata,
    const double *gdata,
    double t)
{
  return gdata[DISMORTALITY] * u[I];

}


/**
 *  carriers to susceptible: C -> S (NEW)
 *
 * @param u The compartment state vector in node.
 * @param v The continuous state vector in node.
 * @param ldata The local data vector for node.
 * @param gdata The global data vector.
 * @param t Current time.
 * @return propensity.
 */
double SISe_sp_C_to_S(
    const int *u,
    const double *v,
    const double *ldata,
    const double *gdata,
    double t)
{
  return gdata[TAU] * u[C];

}
```

```
/**
 *  disease death to susceptible (restocking): D -> S (NEW)
 *
 * @param u The compartment state vector in node.
 * @param v The continuous state vector in node.
 * @param ldata The local data vector for node.
 * @param gdata The global data vector.
 * @param t Current time.
 * @return propensity.
 */
double SISe_sp_D_to_S(
    const int *u,
    const double *v,
    const double *ldata,
    const double *gdata,
    double t)
{
  return gdata[RESTOCK] * u[D];

}
```

```
/**
 * Update environmental infectious pressure phi
 *
 * Decay environmental infectious pressure phi, add contribution from
 * infected individuals, carriers and proximity coupling.
 * @param v_new The continuous state vector in the node after the post
 * time step
 * @param u The compartment state vector in the node.
 * @param v The current continuous state vector in the node.
 * @param ldata The local data vector for the node.
```

```
 * @param gdata The global data vector.
 * @param node The node.
 * @param t The current time.
 * @return error code (<0), or 1 if node needs to update the
 * transition rates, or 0 when it doesn't need to update the
 * transition rates.
 */
int SISe_sp_post_time_step(
    double *v_new,
    const int *u,
    const double *v,
    const double *ldata,
    const double *gdata,
    int node,
    double t)
{
    const int day = (int)t % 365;
    const double I_i = u[I];
    const double C_i = u[C];
    const double N_i = u[S] + I_i + C_i; /* added in C_i here because it contributes
to environmental infectious pressure. The other new compartments do not.*/
    const double phi = v[PHI];
    const int Nc = 5;

    /* Determine the pointer to the continuous state vector in the
     * first node. Use this to find phi at neighbours to the current
     * node. */
    const double *phi_0 = &v[-node];

    /* Determine the pointer to the compartment state vector in the
     * first node. Use this to find the number of individuals at
     * neighbours to the current node. */
    const int *u_0 = &u[-Nc*node];
```

```
    /* Time dependent decay (beta) of the environmental infectious
     * pressure in each of the four intervals of the year. Forward
     * Euler step. */
    v_new[PHI] = SimInf_forward_euler_linear_decay(
        phi, day,
        ldata[END_T1], ldata[END_T2], ldata[END_T3], ldata[END_T4],
        gdata[BETA_T1], gdata[BETA_T2], gdata[BETA_T3], gdata[BETA_T4]);

    /* Local spread among proximal nodes. */
        /* Have added in the part of the local equation that includes infection from
carriers */
    if (N_i > 0.0) {
        v_new[PHI] += (gdata[ALPHA] * I_i) + (gdata[EPAR] * gdata[ALPHA] *
C_i)/ N_i +
            SimInf_local_spread(&ldata[NEIGHBOR], phi_0, u_0,
                                N_i, phi, Nc, gdata[COUPLING]);
    }

    if (!R_FINITE(v_new[PHI]))
        return SIMINF_ERR_V_IS_NOT_FINITE;
    if (v_new[PHI] < 0.0)
        return SIMINF_ERR_V_IS_NEGATIVE;
    return phi != v_new[PHI]; /* 1 if needs update */
}

/**
 * Run simulation with the SISe_sp model
 *
 * @param model The SISe_sp model.
 * @param threads Number of threads.
 * @param solver The numerical solver.
 * @return The simulated trajectory.
 */
SEXP SISe_sp_run(SEXP model, SEXP threads, SEXP solver)
```

```
{
    TRFun tr_fun[] = {&SISe_sp_S_to_I, &SISe_sp_I_to_S, &SISe_sp_I_to_C,
                      &SISe_sp_I_to_D, &SISe_sp_C_to_S, &SISe_sp_D_to_S};

    return SimInf_run(model, threads, solver, tr_fun, &SISe_sp_post_time_step);
```

The following is the adapted R code for the SISe_sp model with comments and changes I have made highlighted in red:

```
## This file is part of SimInf, a framework for stochastic
## disease spread simulations.
##
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##
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##' Definition of the \code{SISe_sp} model
##'
##' Class to handle the \code{SISe_sp} \code{\link{SimInf_model}}.
##' @include SimInf_model.R
##' @export
setClass("SISe_sp", contains = c("SimInf_model"))

##' Create a \code{SISe_sp} model
##'
##' Create a \code{SISe_sp} model to be used by the simulation
##' framework.
##'
##' The \code{SISe_sp} model contains two compartments; number of
##' susceptible (S) and number of infectious (I). Additionally, it
##' contains an environmental compartment to model shedding of a
##' pathogen to the environment. Moreover, it also includes a spatial
##' coupling of the environmental contamination among proximal nodes
##' to capture between-node spread unrelated to moving infected
##' individuals. Consequently, the model has two state transitions,
##'
##' \deqn{S \stackrel{\upsilon \varphi S}{\longrightarrow} I}{
##' S -- upsilon phi S --> I}
##'
##' \deqn{I \stackrel{\gamma I}{\longrightarrow} S}{
##' I -- gamma I --> S}
##'
```

```
##' where the transition rate per unit of time from susceptible to
##' infected is proportional to the concentration of the environmental
##' contamination \eqn{\varphi}{phi} in each node. Moreover, the
##' transition rate from infected to susceptible is the recovery rate
##' \eqn{\gamma}, measured per individual and per unit of
##' time. Finally, the environmental infectious pressure in each node
##' is evolved by,
##'
##' \deqn{\frac{d \varphi_i(t)}{dt} = \frac{\alpha I_{i}(t)}{N_i(t)} +
##' \sum_k{\frac{\varphi_k(t) N_k(t) - \varphi_i(t) N_i(t)}{N_i(t)}
##' \cdot \frac{D}{d_{ik}}} - \beta(t) \varphi_i(t)}{
##' dphi(t)/dt=
##' alpha I / N +
##' D*sum_k(phi_k*N_k-phi_i*N_i)/(d_ik*N_i)-beta*phi_i}
##'
##' where \eqn{\alpha} is the average shedding rate of the pathogen to
##' the environment per infected individual and \eqn{N = S + I} the
##' size of the node. Next comes the spatial coupling among proximal
##' nodes, where \eqn{D} is the rate of the local spread and
##' \eqn{d_{ik}} the distance between holdings \eqn{i} and
##' \eqn{k}. The seasonal decay and removal of the pathogen is
##' captured by \eqn{\beta(t)}. The environmental infectious pressure
##' \eqn{\varphi(t)}{phi(t)} in each node is evolved each time unit by
##' the Euler forward method. The value of \eqn{\varphi(t)}{phi(t)} is
##' saved at the time-points specified in \code{tspan}.
##'
##' The argument \code{u0} must be a \code{data.frame} with one row for
##' each node with the following columns:
##' \describe{
##' \item{S}{The number of sucsceptible}
##' \item{I}{The number of infected}
##' }
##'
##' @template beta-section
##' @template u0-param
##' @template tspan-param
##' @template events-param
##' @template phi-param
##' @param upsilon Indirect transmission rate of the environmental
##'    infectious pressure
##' @param epar This is the scaling rate for Carrier's contribution to transmission
##' @param tau this is the recovery rate for carriers
##' @param qprop this is the scaling rate for infecteds that become carriers
##' @param dismortality the disease mortality rate
##' @param restock the restocking rate
##' @param gamma The recovery rate from infected to susceptible
##' @param alpha Shed rate from infected individuals
##' @template beta-param
##' @param coupling The coupling between neighboring nodes
##' @param distance The distance matrix between neighboring nodes
##' @return \code{SISe_sp}
```

```
##' @include check_arguments.R
##' @export
##' @importFrom methods as
##' @importFrom methods is
SISe_sp <- function(u0,
                    tspan,
                    events   = NULL,
                    phi      = NULL,
                    upsilon  = NULL,
                    gamma    = NULL,
                    alpha    = NULL,
                    epar     = NULL, #new parameter epar here - this is the scaling rate for
Carriers transmission
                    tau      = NULL, #new - this is the recovery rate for Carriers
                    qprop    = NULL, #new - this is equivalent to q in my notes. This helps
scale the proportion of infecteds that recover and then become carriers
                dismortality = NULL, #new - disease mortality. Moves infected
individuals (assumed carriers won't die) to the "dead" compartment
                   restock   = NULL, #restocks from the dead compartment
                    beta_t1  = NULL,
                    beta_t2  = NULL,
                    beta_t3  = NULL,
                    beta_t4  = NULL,
                    end_t1   = NULL,
                    end_t2   = NULL,
                    end_t3   = NULL,
                    end_t4   = NULL,
                    coupling = NULL,
                    distance = NULL) {
  compartments <- c("S", "I", "C", "D", "H") #added in C for carriers and H for
treated individuals. D is the restocking compartment

  ## Check arguments.

  ## Check u0 and compartments
  u0 <- check_u0(u0, compartments)

  ## Check initial infectious pressure
  if (is.null(phi))
    phi <- 0
  phi <- rep(phi, length.out = nrow(u0))
  check_infectious_pressure_arg(nrow(u0), phi)

  ## Check for non-numeric parameters
  check_gdata_arg(upsilon, gamma, alpha, epar, tau, qprop, dismortality, restock,
beta_t1, beta_t2, beta_t3, beta_t4,
                  coupling) #added in new parameters

  ## Check interval endpoints
  check_integer_arg(end_t1, end_t2, end_t3, end_t4)
  end_t1 <- rep(end_t1, length.out = nrow(u0))
```

```
  end_t2 <- rep(end_t2, length.out = nrow(u0))
  end_t3 <- rep(end_t3, length.out = nrow(u0))
  end_t4 <- rep(end_t4, length.out = nrow(u0))
  check_end_t_arg(nrow(u0), end_t1, end_t2, end_t3, end_t4)

  check_distance_matrix(distance)

  ## Arguments seem ok...go on

  E <- matrix(c(1, 0, 0, 0, 0, 1, 1, 1, 0, 0, 0, 0, 0, 0, 1, 1,1,1,0,1), nrow = 5, ncol = 4,
           dimnames = list(compartments, c("1", "2", "3", "4"))) #adapted this for
the new model
  N <- matrix(c(4,3,2,0,0,0,0,0,0,-4), nrow = 5, ncol = 2, dimnames =
list(compartments, c("1", "2"))) #added this in – indicates how sampled individuals
are shifted between compartments during scheduled internal events.

  G <- matrix(c(rep(1,36)), nrow = 6, ncol = 6,
           dimnames = list(c("S -> upsilon*phi*S -> I",
                             "I -> gamma*((1-qprop)*I) -> S",
                             "I -> gamma*qprop*I -> C",
                             "I -> mortality*I -> D",
                             "C -> tau*C -> S",
                             "D -> restock*D ->S"),
                           c("1", "2", "3", "4", "5", "6"))) #adapted this for the new model

  S <- matrix(c(-1, 1, 0, 0, 0, 1, -1, 0,0,0,0,-1,1,0,0,0,-1,0,1,0,1,0,-1,0,0,1,0,0,-1,0),
nrow = 5, ncol = 6,
           dimnames = list(compartments, c("1", "2", "3", "4", "5", "6"))) #adapted
this for the new model.

  v0 <- matrix(as.numeric(phi), nrow  = 1, byrow = TRUE,
           dimnames = list("phi"))

  ldata <- matrix(as.numeric(c(end_t1, end_t2, end_t3, end_t4)),
              nrow = 4, byrow = TRUE,
              dimnames = list(c("end_t1", "end_t2", "end_t3", "end_t4")))
  ldata <- .Call(SimInf_ldata_sp, ldata, distance, 1L)

  gdata <- as.numeric(c(upsilon, gamma, alpha, epar, tau, qprop, dismortality,
restock, beta_t1, beta_t2,
                      beta_t3, beta_t4, coupling)) #added in new parameters here
  names(gdata) <- c("upsilon", "gamma", "alpha", "epar", "tau", "qprop",
"dismortality", "restock", "beta_t1", "beta_t2",
                  "beta_t3", "beta_t4", "coupling")

  model <- SimInf_model(G      = G,
                        S      = S,
                        E      = E,
                        N      = N,
                        tspan  = tspan,
                        events = events,
```

```
                    ldata  = ldata,
                    gdata  = gdata,
                    u0     = u0,
                    v0     = v0)

  as(model, "SISe_sp")
}
```

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Version 3, 29 June 2007

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parties to make or receive copies. Mere interaction with a user through
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the interface presents a list of user commands or options, such as a
menu, a prominent item in the list meets this criterion.

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  The "source code" for a work means the preferred form of the work
for making modifications to it. "Object code" means any non-source
form of a work.

  A "Standard Interface" means an interface that either is an official
standard defined by a recognized standards body, or, in the case of
interfaces specified for a particular programming language, one that
is widely used among developers working in that language.

  The "System Libraries" of an executable work include anything, other
than the work as a whole, that (a) is included in the normal form of
packaging a Major Component, but which is not part of that Major
Component, and (b) serves only to enable use of the work with that
Major Component, or to implement a Standard Interface for which an
implementation is available to the public in source code form. A

"Major Component", in this context, means a major essential component
(kernel, window system, and so on) of the specific operating system
(if any) on which the executable work runs, or a compiler used to
produce the work, or an object code interpreter used to run it.

  The "Corresponding Source" for a work in object code form means all
the source code needed to generate, install, and (for an executable
work) run the object code and to modify the work, including scripts to
control those activities. However, it does not include the work's
System Libraries, or general-purpose tools or generally available free
programs which are used unmodified in performing those activities but
which are not part of the work. For example, Corresponding Source
includes interface definition files associated with source files for
the work, and the source code for shared libraries and dynamically
linked subprograms that the work is specifically designed to require,
such as by intimate data communication or control flow between those
subprograms and other parts of the work.

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    (including a physical distribution medium), accompanied by a
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    product that is covered by this License, on a durable physical

    medium customarily used for software interchange, for a price no
    more than your reasonable cost of physically performing this
    conveying of source, or (2) access to copy the
    Corresponding Source from a network server at no charge.

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    only if you received the object code with such an offer, in accord
    with subsection 6b.

    d) Convey the object code by offering access from a designated
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    copy the object code is a network server, the Corresponding Source
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protocols for communication across the network.

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